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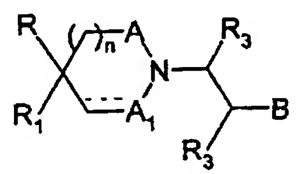
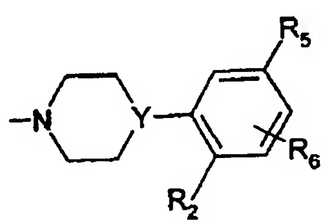
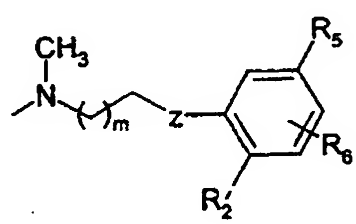
(54) Title: CYCLIC AMIDES AND IMIDES HAVING SELECTIVE ANTAGONIST ACTIVITY AT ALPHA-1D ADRENERGIC RECEPTOR



(I)



(B_1)



(B_2)

(57) Abstract: Compounds (I) R and R_1 independently = H or C_1-C_4 alkyl or together = $(CH_2)_{2-6}$, n=0 or 1, ... is a single or a double bond, A=CO or CH_2, A_1 represents a CO or CH_2 or CH, each R_3 independently = H or C_1-C_4 alkyl, B is B_1 or B_2 (B_2); Y=N or CH, R_2 = halogen, C_1-C_4 alkyl or CN, R_5 = halogen, C_1-C_4 alkyl, polyfluoroalkyl or NO_2, R_6 = H or halogen, m is 1 to 3, Z = O, S, NH or NMe) interact selectively with the α_{1D} subtype of the α_1 adrenergic receptor. This selectively makes these compounds useful agents in tissues particularly rich in α_{1D} adrenergic receptors, thus useful in reducing contractility of an unstable urinary bladder, in the treatment and prevention of atherosclerosis as they are inhibitors of noradrenaline-mediated cell proliferation in smooth muscles, and in reducing vascular adrenergic tone. The preparation of these compounds, their enantiomers, diastereoisomers, N-oxides and pharmaceutically acceptable salts, and pharmaceutical compositions containing them are also claimed.

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— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

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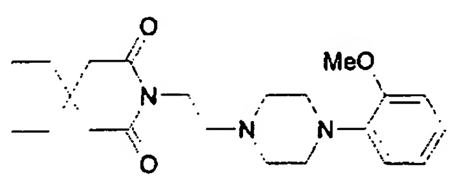
TITLE

CYCLIC AMIDES AND IMIDES HAVING SELECTIVE ANTAGONIST ACTIVITY AT ALPHA-1D ADRENERGIC RECEPTOR

DESCRIPTION

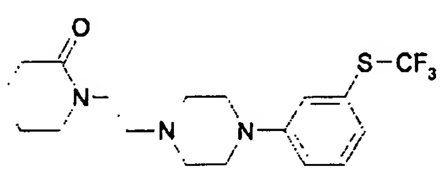
BACKGROUND OF THE INVENTION

N,ω-aminoalkyl cyclic imides are reported in the scientific literature and among them the most investigated for its pharmacological activity at the adrenergic receptor is BMY 7378.



BMY 7378

This molecule was first described by Y-H. Wu et al. in *J. Med. Chem* 12, 876-881 (1969) and later investigated as a serotonergic-$5HT_{1A}$-receptor putative antagonist by T. Sharp et al., *Eur. J. Pharmacol.* 176, 331-340 (1990). More recently, A. S. Goetz et al., *Eur. J. Pharmacol.* 272, R5-R6 (1995) reported for BMY 7378 a selective antagonism for the D subtype of the α1-adrenergic receptor. Another N, ω-aminoalkyl cyclic amide is



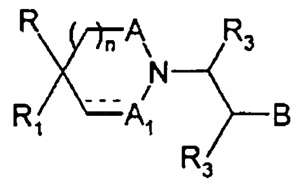
which is described in GB 2,023,594, where use as antidepressant is foreseen for it.

The compounds of the invention, described below, essentially include a different substitution pattern at the phenylpiperazine group and also a larger structural variability of the imido and amido rings.

These structural variations give the new compounds the ability to bind and interact selectively with the α_{1D} subtype of the adrenergic receptor, this selectivity also limiting interaction with the 5-HT_{1A} serotoninergic receptor, differently from the previously-known α_{1D}-adrenoceptor-"selective" antagonist named BMY 7378, which is endowed with very high affinity for this serotonergic receptor and hence is devoid of selectivity for α_{1D} vs. 5-HT_{1A} receptors as shown below in Table 1 in Example 33.

SUMMARY OF THE INVENTION

In one aspect the invention is directed to compounds of formula I.



(I)

wherein

each of R and R_1 independently represents a hydrogen atom or a lower alkyl group having from 1 to 4 carbon atoms, or R and R_1 together form an alkylene bridge ($(CH_2)_{2-6}$);

n is an integer from 0 to 1;

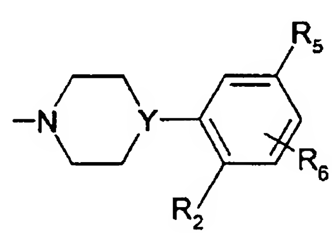
...... represents a single or a double bond;

A represents a carbonyl group or a methylene group;

A_1 represents a carbonyl group or a methylene group or a methyne group;

each R_3 independently represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms;

B represents one of the following groups:



(B_1)

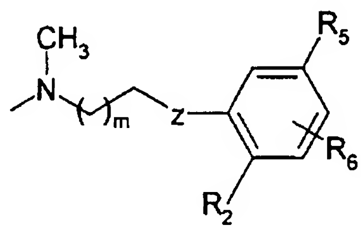
wherein:

Y represents a nitrogen atom or a methyne group;

R_2 represents a halogen atom or a lower alkyl group (C_1-C_4) or a cyano group;

R_5 represents a halogen atom or a lower alkyl group (C_1-C_4) or a polyfluoroalkyl group or a nitro group;

R_6 represents a hydrogen or halogen atom;



(B_2)

wherein

m is an integer from 1 to 3;

Z represents an oxygen or sulphur atom or an amino or methylamino group;

R_2, R_5 and R_6 have the above meanings;

with the proviso that not more than one of R_2, R_5 and R_6 represents a fluorine atom if R and R_1 together form an alkylene bridge, A and A_1 both represent carbonyl groups, n is 1, the heterocyclic ring is saturated and Y represents a nitrogen atom.

Preferably R_3 represents a hydrogen atom or a methyl group.

Preferably R_2 represents a fluorine, chlorine, bromine or iodine atom or a methyl or cyano group.

Preferably R_5 represents a fluorine, chlorine, bromine or iodine atom or a trifluoromethyl or nitro group.

Preferably R_6 represents a hydrogen atom or a fluorine atom at position 4 of the phenyl ring.

Preferably R and R_1 together represent a trimethylene, tetramethylene, pentamethylene or hexamethylene group.

Preferably A and A_1 both represent carbonyl groups, or one of A and A_1 represents a carbonyl group and the other of A and A_1 is a methylene unit.

Preferably B represents a B_1 group wherein Y is a nitrogen atom, R_2 and R_5 both represent chlorine atoms.

The invention further provides pharmaceutical compositions comprising a compound of formula I, an enantiomer, diastereoisomer, N-oxide or pharmaceutically acceptable salt of such a compound in admixture with a pharmaceutically acceptable diluent or carrier.

In another aspect the present invention is directed to methods for reducing contractility of the unstable bladder, by reducing adrenergic vascular tone and inhibiting noradrenaline-mediated smooth-muscle cell proliferation, all by administering a compound of formula I to a mammal (including a human) in need of such treatment in an amount or amounts effective for the particular use.

In yet another aspect, the invention is directed to methods for blocking selectively the α_{1D} adrenoceptor, by delivering to the environment of said receptor, e.g. to the extracellular medium, or by administering to a mammal possessing said receptors, an effective amount of a compound of the invention.

DETAILED DESCRIPTION OF THE INVENTION

All patents, patent applications, and literature references cited in this application are incorporated by reference in their entirety.

The adrenergic antagonistic activity of the compounds of the invention renders them useful as agents acting on body tissues particularly rich in α_{1D}-adrenergic receptors (such as urinary bladder, blood vessels, etc.). Accordingly, selective antiadrenergic compounds within the invention established as such on the basis of their receptor binding profile, can be useful therapeutic agents for the treatment, for example, of micturition problems associated with unstable bladder and cardiovascular problems due to skeletal-muscle arteriole constriction, or to inhibit smooth-muscle cell proliferation, such as in atherosclerosis.

Pharmacological, biochemical and radioligand binding studies evidenced three different α_1-receptors subtypes with a high affinity for prazosin, namely α_{1A}- (α_{1a}-), α_{1B}- (α_{1b}-) and α_{1D}- (α_{1d}-), with lower case subscripts being used for recombinant receptors and upper case subscripts for receptors in native tissues (Hieble et al., Pharmacol. Rev. 47: 267-270, (1995)).

The functional involvement of α_{1D}-adrenoceptor in detrusor instabilty secondary to bladder outlet obstruction has been recently reported (T. Broten et al., FASEB Journal 12 (4), A445 (1998)). The relevance of the α_{1D} adrenergic subtype in mediating constriction of rat skeletal muscle arterioles was reported by C. J. Leech et al. (Am. J. Physiol. 270, 4710-722 (1996) and mediation by the α_{1D} adrenoceptor of protein synthesis in arterial smooth muscle leading to abnormal smooth-muscle cell growth was also reported by Xin et al., Mol. Pharmacol. 51, 764-775 (1997).

The selectivity of the compounds of the invention for the α_{1D} receptor should make them effective in the above cited diseases, such as urinary incontinence, vasoconstriction and atherosclerosis, without inducing significant undesired effects on blood pressure, due also to their lower affinity for the 5-HT_{1A} serotonergic receptors. Indeed urapidil (6-{[3-[4-(2-methoxyphenyl)-1-piperazinyl]-propyl]-amino}-1,3-dimethyl-2,4(1*H*,3*H*)-pyrimidinedione), an α_1-antagonist with no selectivity for the α_1 subtypes and good affinity for the 5-HT_{1A} receptor, is known to reduce blood pressure by

sympathoinhibitory action caused by activation of 5-HT_{1A} receptors (A. G. Ramage, *Brit. J. Pharmacol.* 102, 998-1002 (1991)). Hence, compounds of the invention could be used without causing undesired hypotensive effects and without interfering with the effect of antihypertensive drugs, when this therapy is needed.

Screening candidate compounds to identify compounds useful in practising the present invention involves measuring the specific binding activity of the compounds towards the different α_1-adrenergic-receptor subtypes, namely the α_{1a}, α_{1b} and α_{1d} subtypes, according to the method of Testa et al., *Pharmacol. Comm.* 6, 79-86 (1995). By this method a measure of affinity to the human recombinant subtypes of the α_1 adrenoceptor by radioreceptor binding can be obtained.

A detailed description is given in Example 32, where measurement of affinity for the 5-HT_{1A} receptor evaluated by the same approach (radioreceptor binding on recombinant human receptor) is also described.

In addition to affinity by radioreceptor binding also functional antagonism at the α_1 adrenoceptor subtypes can be evaluated, in order to confirm functional selectivity of the compounds of the invention. To this purpose, inhibition of contraction induced by an α_1 adrenoceptor agonist in selected organs or tissues can be assessed. In particular by using noradrenaline and the following tissues, affinity for the α_1 adrenoceptor subtypes can be evaluated:

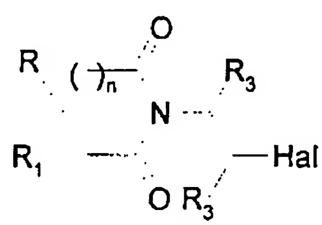
- rat aorta, α_{1D} subtype (Testa R. et al., Life Sci. 57, PL159, 1995).
- epididymal rat vas deferens, α_{1A} subtype (Burt R. P. et al., Br. J. Pharmacol. 115, 467 (1995)).
- guinea pig spleen, α_{1B} subtype (Eltze M., Eur. J. Pharmacol. 260, 211 (1994)).
- rabbit aorta preincubated with CEC, α_{1L} subtype (Oshita M. et al., Br J. Pharmacol. 108, 1071 (1993)).

A detailed description of the functional affinity evaluation for the compounds of the invention is given in Example 33.

Once a compound is identified as possessing the desired selectivity characteristics, namely an affinity for the α_{1d} subtype at least 10-fold higher than for the other studied receptors, its pharmacological activity can be confirmed using one or more animal model systems for studying urinary incontinence. A useful animal model system includes without limitation, cystometry in bladder-outlet obstructed rats. The details of this model are given in Example 34.

The compounds of the invention may be prepared by a number of methods known in the art from known starting materials or starting materials that may be prepared by conventional methods.

One method of preparing the cyclic imides of the invention comprises alkylating an amine BH, in which B may be B_1 or B_2, with a haloalkyl intermediate of formula

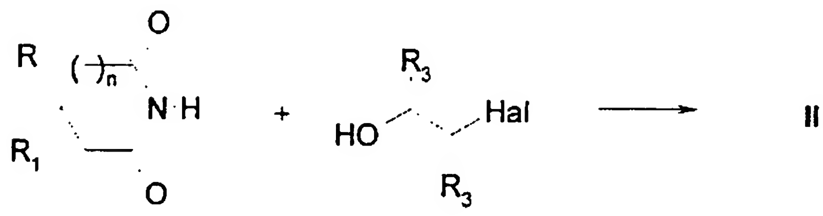


(II)

where R, R_1, R_3 and n have the meanings given above and Hal can be, for example, a bromine or chlorine atom. The reaction may be carried out without solvent, in the presence of a base, such as triethylamine (TEA) or diisopropylethylamine (DIPEA), at 100-180°C.

The starting intermediates II, in which R_3 is hydrogen, may be prepared by methods known in the literature, starting from the corresponding imides and 1,2-dihaloethanes. Intermediates II, in which one of R_3 is a lower alkyl group may be prepared by a process such as that exemplified below:

Scheme 1

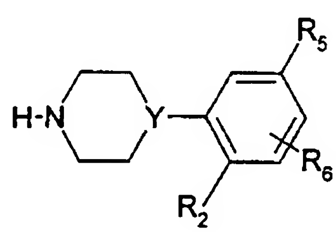


III IV

where R, R_1 and n are as defined above, and Hal represents a halogen atom, particularly a chlorine or bromine atom.

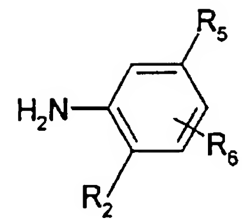
The intermediate imides III may be reacted with haloalcohols IV under Mitsunobu conditions using triphenylphosphine and diethyl azodicarboxylate in a polar aprotic solvent, such as dimethylformamide (DMF) or tetrahydrofuran (THF), at 10-80°C.

Intermediates BH in which B is B_1 as follows:



(B_1H)

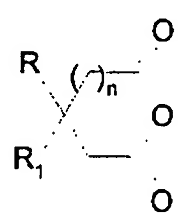
wherein Y is nitrogen and R_2, R_5 and R_6 have the meanings as defined above, are commercially available or may be prepared starting from the corresponding anilines



by reaction with *bis*-2-chloroethylamine in the presence of a base, such as sodium or potassium carbonate, and of a promoter, such as potassium iodide, in a polar protic solvent, such as *n*-butyl alcohol or *i*-amyl alcohol. at reflux temperature. Non-commercially-available anilines may be prepared by reduction of the corresponding nitro compounds by methods well known in the literature, for example by using tin (II) chloride in refluxing alcohols.

Intermediates B_1H as above may also be prepared starting from the corresponding piperazines in which R_5 and R_6 are hydrogen. For example B_1H in which R_5 is iodine may be prepared by iodination of the appropriate arylpiperazine using iodine chloride in a polar protic solvent, such as acetic acid, at 10-40°C.

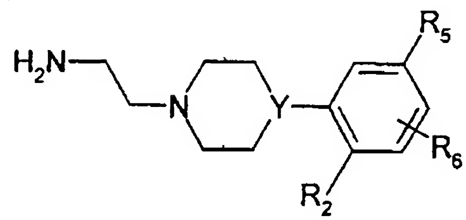
Another method of preparing the compounds of the invention comprises acylating an amine $BCH_2CH_2NH_2$, in which B is B_1 or B_2, with an anhydride of formula



where R, R_1 and n have the meanings given above.

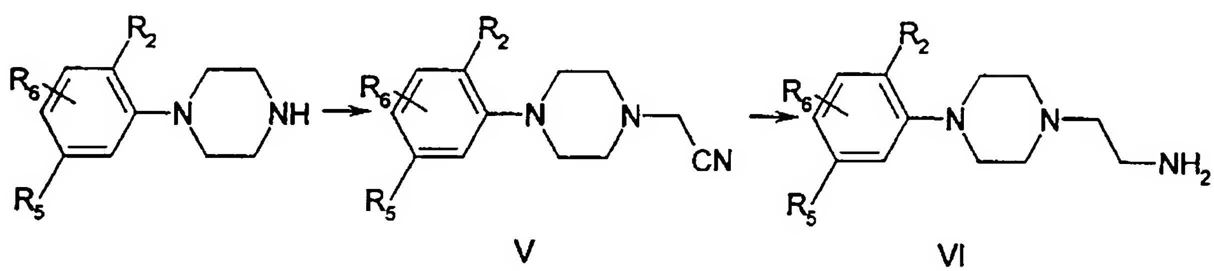
The reaction may be carried out in an apolar aprotic solvent, such as toluene, in the presence of a promoting agent, such as *p*-toluenesulphonic acid, at 80°C to reflux.

Intermediates $BCH_2CH_2NH_2$, in which B is B_1 of the formula:



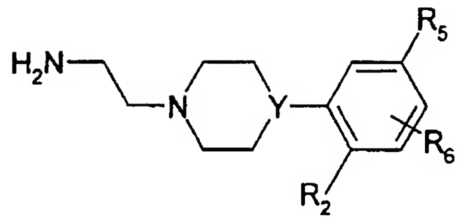
in which Y is nitrogen and R_2, R_5 and R_6 have the meanings defined above, may be prepared according to the following scheme 2.

Scheme 2



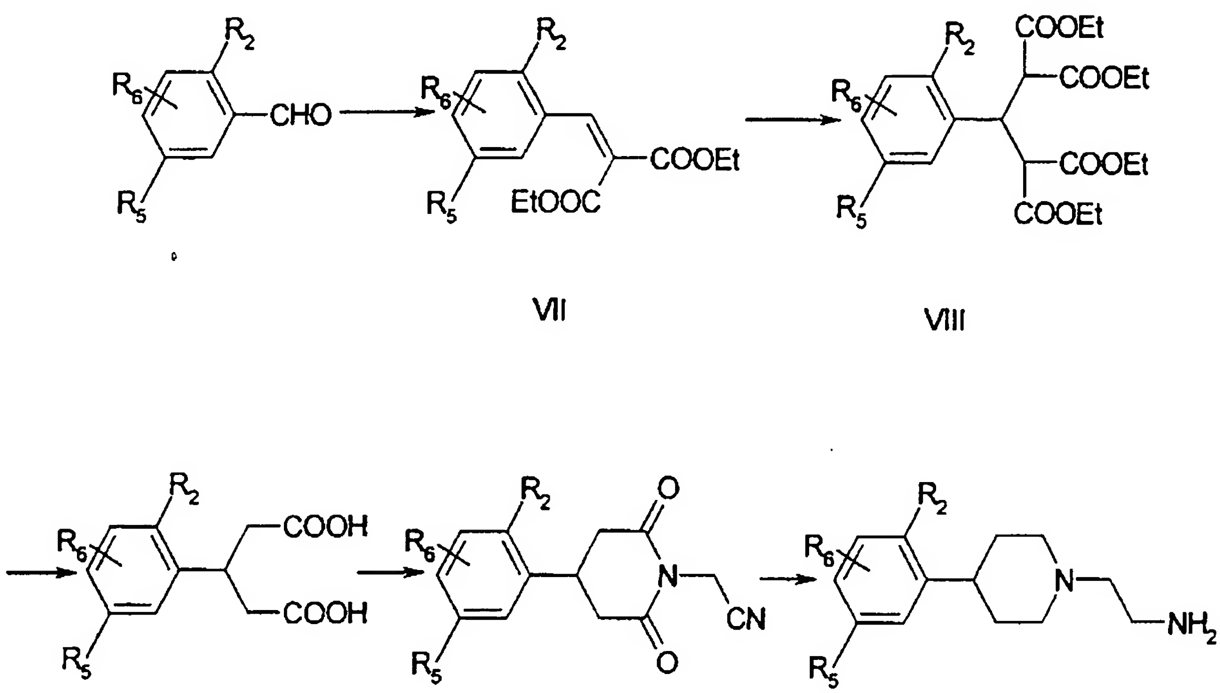
The appropriate arylpiperazines may be alkylated with chloroacetonitrile to give intermediates V. The reaction may be carried out in an aprotic apolar solvent, such as toluene, or in a polar solvent, such as DMF, un the presence of a base, such as potassium carbonate or DIPEA, at 60-120°C. Intermediates V can then be reduced to amines VI. The reaction may be carried out using a reducing agent, such as $LiAlH_4$ or BH_3-Me_2S, in a polar aprotic solvent, such as diethyl ether or THF, at –10/20°C.

Intermediates $BCH_2CH_2NH_2$, in which B is B_1, of the formula:



where Y is CH and R_2, R_5 and R_6 have the meanings defined above, may be prepared according to the following Scheme 3.

Scheme 3



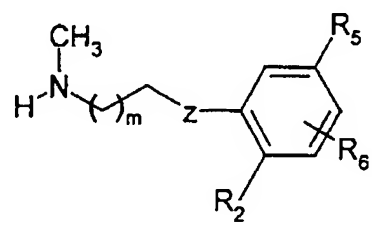
VII VIII

IX X XI

The appropriate aldehydes may be reacted with diethyl malonate in the presence of a Lewis acid, such as $AlCl_3$, without solvent, at 0-30°C, to give intermediates VII, which are further reacted with diethyl malonate at a higher temperature (at 40-100°C) to give intermediates VIII. The following decarbethoxylation can be carried out in an acidic

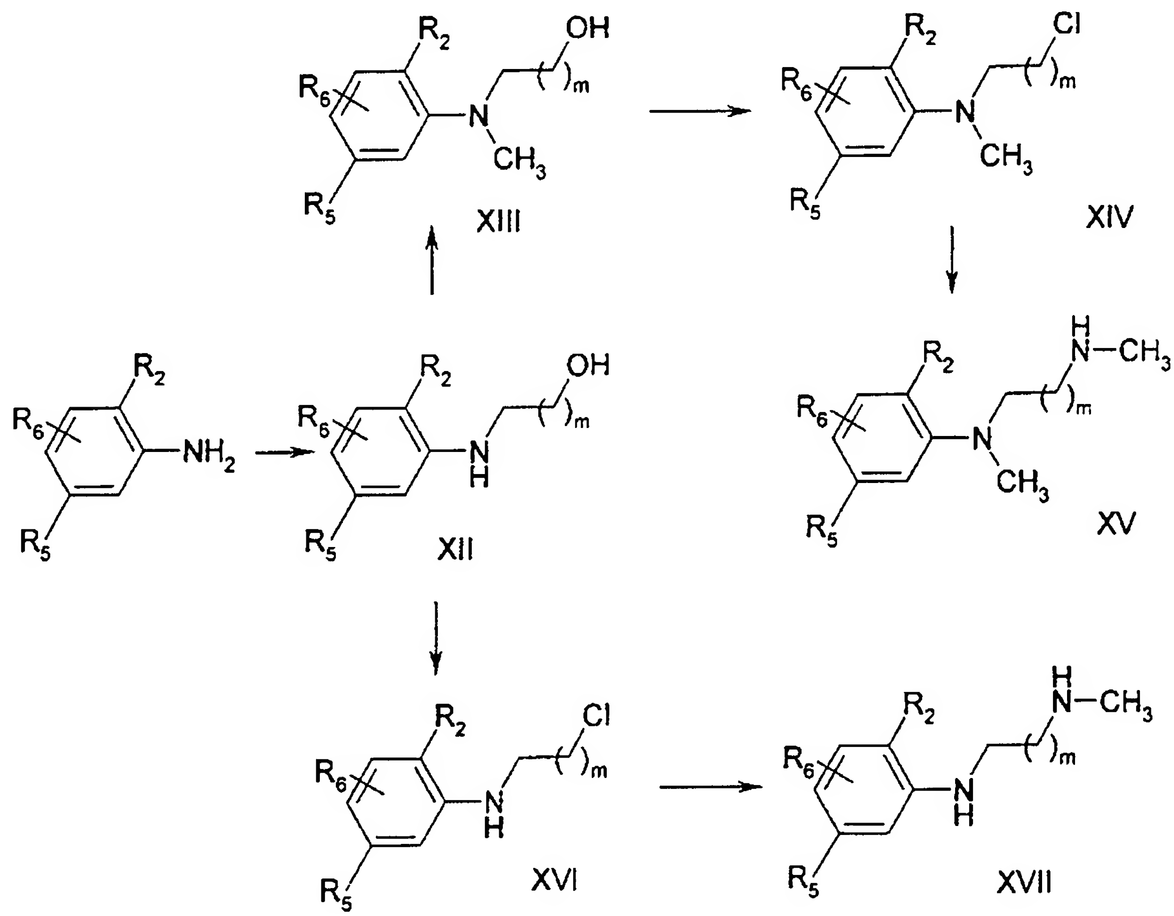
medium, such as HBr, in water at 80°C to reflux. The diacid intermediate IX may be condensed with aminoacetonitrile in the presence of a condensing agent, such as dicyclohexylcarbodiimide (DCC), in the presence of a base, such as TEA, in a polar aprotic solvent, such as DMF, at 10-40°C, with treatment of the crude in dehydrating conditions, such as acetic anhydride, at 80-110°C, to give intermediates X. These intermediates may be reduced using a metal hydride, such as $LiAlH_4$ or BH_3-Me_2S, in a polar aprotic solvent, such as diethyl ether or THF, at 20°C to reflux to give intermediates XI.

Intermediates BH, in which B is B_2 of the formula:



in which m, R_2, R_5 and R_6 have the meanings defined above and Z is NH or NCH_3, may be prepared according to the following scheme 4.

Scheme 4

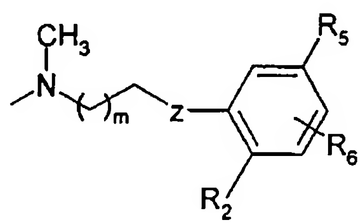


The appropriate anilines may be alkylated by an □-haloalkyl alcohol (Hal-$CH_2(CH_2)_m$-OH) in the presence of a proton acceptor, such as TEA, at 100-160°C without solvent to give intermediates XII. Intermediates XII are then N-methylated to give the tertiary amines XIII. This reaction may be carried out using formaldehyde in the presence of a reducing agent, such as formic acid, in a polar solvent, such as water, at 100-120°C.

The intermediate aminoalcohols XII and XIII are independently chlorinated to give intermediates XVI and XIV. The reaction may be carried out using a chlorinating agent, such as $SOCl_2$, in a chlorinated solvent, such as chloroform or dichloromethane, in the presence of a promoter, such as DMF, at 20°C to reflux. Intermediates XIV and XVI are

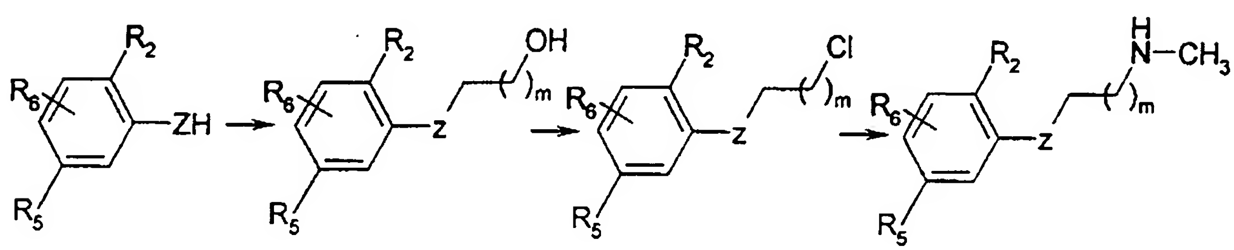
then used to alkylate methylamine to give intermediates XV and XVII respectively. The reaction may be carried out in an autoclave at 60-100°C without solvent.

Intermediates BH, in which B is B_2, as follows:



where m, R_2, R_5 and R_6 have the meanings defined above and Z is oxygen or sulphur, may be prepared according to the following scheme 5.

Scheme 5



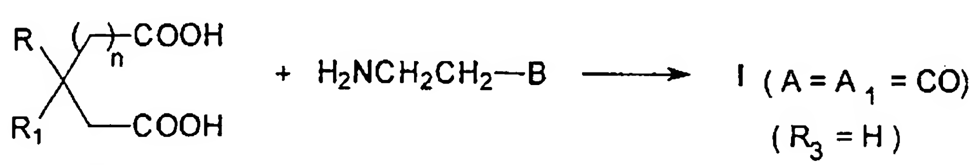
XVIII XIX XX

The appropriate phenols or thiophenols may be alkylated by Hal-$CH_2(CH_2)_m$-OH in an apolar aprotic solvent such as toluene, or in a polar one such as DMF, optionally in the presence of a proton acceptor, such as TEA or potassium carbonate, at 80-120°C to give intermediates XVIII. These are chlorinated to give XIX and used to alkylate methylamine to give XX using the conditions described for analogues in scheme 4.

Type B_2 intermediates of formula XV, XVII or XX may be converted into the corresponding derivatives of formula B_2-$CH_2CH_2NH_2$ using the same synthetic methods shown in scheme 2 for the B_1H piperazine derivatives.

Another method of preparing the compounds of the invention is exemplified in the following scheme 6.

Schema 6



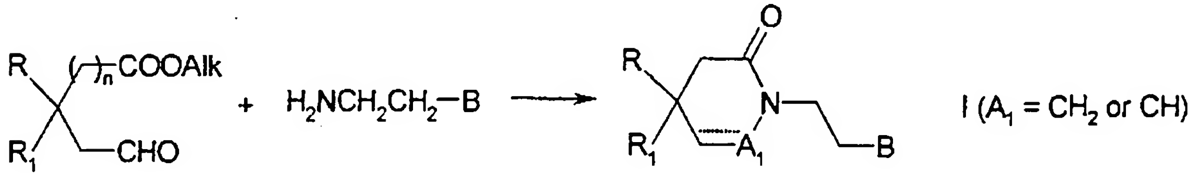
XXI

where R, R_1, n and B have the meanings defined above.

The reaction may be carried out first by amidification in the presence of a condensing agent, such as DCC, in a polar aprotic solvent, such as DMF, at 10-40°C, followed by dehydratation using an anhydride, such as acetic anhydride, without solvent at 80-120°C.

Another method of preparing the compounds of the invention is depicted in the following scheme 7.

Scheme 7



XXII

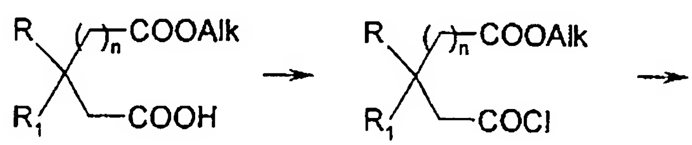
where R, R_1 and B have the meanings defined above, Alk is a lower alkyl group (C_{1-2}) and n is 1.

To obtain compounds I in which ...... is a single bond and A_1 is a methylene group, the reaction may be carried out under reductive conditions using a metal borohydride, such as $NaBH_4$, in a polar protic solvent, such as methanol, at –5/25°C.

To obtain compounds in which ...... is a double bond and A_1 is a methyne group the reaction may be carried out in an apolar aprotic solvent, such as toluene, in the presence of an acid catalyst, such as *p*-toluenesulphonic acid, at reflux temperature distilling the azeotrope.

Intermediates XXII as defined above may be prepared according to the following scheme 8.

Scheme 8

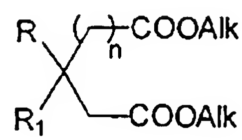


XXII

XXIII

The appropriate diacid monoesters are chlorinated to give intermediates XXIII. The reaction may be carried out using a chlorinating agent, such as $SOCl_2$ or oxalyl chloride, in a polar aprotic solvent, such as dichloromethane or toluene, in the presence of catalytic amounts of a promoting agent, such as DMF, at 5-25°C. These intermediates are then reduced to give XXII. This reaction may be carried out using a reducing agent, such as hydrogen, in a polar aprotic solvent, such as acetone, in the presence of a catalyst, such as palladium on charcoal, and of a base, such as TEA or DIPEA, at 10-25°C.

In a further method for the preparation of the compounds of the invention, a diester of the general formula



where R, R_1 and n are as above defined is condensed with an amine $BCH_2CH_2NH_2$ in which B is as above defined. The condensation may be effected without solvent at a temperature ranging from 80 to 160°C.

A method of preparing the compounds of the invention in which A and A_1 are methylene groups and ...... is a single bond consists of a reduction of compounds I in which A and A_1 are carbonyl groups. The reaction may be carried out using a metal borohydride, such as $NaBH_4$, in the presence of a Lewis catalyst, such as boron trifluoride etherate, in a polar aprotic solvent, such as THF, at –5/25°C.

SYNTHESIS OF THE COMPOUNDS OF THE INVENTION

Example 1

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

A mixture of 0.27 g (1 mmol) of 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione prepared as described by Podona et al., *J. Med. Chem.* 37, 1779-1793 (1994), 0.34 g (1.5 mmol) of 1-(2,5-dichlorophenyl)-piperazine, prepared according to Ratouis R. et al. *J. Med. Chem.* 8, 104-107 (1965), and 0.15 g (1.5 mmol) of triethylamine (TEA) was heated at 180°C for 30 minutes. After cooling to room temperature, the crude was purified by flash chromatography eluting with toluene:acetone 9:1 to give 0.22 g (51%) of the title compound. M.p. 149-150°C.

^{1}H-NMR ($CDCl_3$, δ): 1.43-1.59 (m, 4H, CH_2s of spiro ring), 1.61-1.78 (m, 4H, CH_2s of spiro ring), 2.60 (s, 4H, 2 CH_2CO), 2.78-2.98 (m, 10H, $CONCH_2\underline{CH_2}N$ and piperazine CHs), 4.10 (t, 2H, $CON\underline{CH_2}CH_2N$), 6.87-6.97 (m, 2H, phenyl H4 and H6), 7.18-7.24 (m, 1H, phenyl H3).

The following salts were also prepared:

monomethanesulphonate hemihydrate, m.p. 189-190°C (CH_3CN).

dimethanesulphonate, m.p. 189-191°C (CH_3CN);

Example 2

1-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-piperidinyl-2,6-dione.

The title compound was prepared according to the method used in Example 1, but using 1-(2-bromoethyl)-piperidinyl-2,6-dione, prepared according to Podona T. et al., *Tetrahedron* 49, 4619-4626 (1993), instead of 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione. Yield 25%.

^{1}H-NMR ($CDCl_3$, δ): 1.83-2.02 (m, 2H, $\underline{CH_2}CH_2CO$), 2.56 (t, 2H, $CONCH_2\underline{CH_2}N$), 2.59-2.78 (m, 8H, , 2 CH_2CO and piperazine CHs), 2.94-3.19 (m, 4H, piperazine CHs), 3.96 (t, 2H, $CON\underline{CH_2}CH_2N$), 6.85-6.99 (m, 2H, phenyl H4 and H6), 7.17-7.26 (m, 1H, phenyl H3).

Example 3

8-{2-[4-(2-Chloro-5-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione.

The title compound was prepared according to the method described in Example 1, but using 1-(2-chloro-5-methylphenyl)-piperazine, prepared according to Thunus L. et al., *Ann. Pharm. Fr.* 38, 353-358 (1980), instead of 1-(2,5-dichlorophenyl)-piperazine. The mixture was heated at 160°C for 30 minutes and purification was carried out by elution with toluene:acetone 97:3. Yield 73%, m.p. 139-140°C.

^{1}H-NMR ($CDCl_3$, δ): 1.47-1.59 (m, 4H, CH_2s of spiro ring), 1.71-1.80 (m, 4H, CH_2s of spiro ring), 2.31 (s, 3H, CH_3), 2.58 (t, 2H, $CONCH_2\underline{CH_2}N$), 2.62 (s, 4H, 2 CH_2CO),

2.64-2.78 (m, 4H, piperazine CHs), 2.97-3.09 (m, 4H, piperazine CHs), 3.98 (t, 2H, CONCH$_2$CH$_2$N), 6.68-6.83 (m, 2H, phenyl CHs), 7.17-7.22 (m, 1H, phenyl CH).

Example 4

8-{2-[4-(2-Fluoro-5-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione.

1-(2-Fluoro-5-methylphenyl)-piperazine (4A)

A mixture of 0.16 g (1 mmol) of 2-fluoro-5-methylaniline, 0.18 g (1 mmol) of *bis*-(2-chloroethyl)-amine hydrochloride, 0.14 g (1 mmol) of potassium carbonate, 0.08 g (0.5 mmol) of potassium iodide and 5 ml of *n*-butyl alcohol was stirred at reflux for 72 hours. After cooling to room temperature, the solvent was evaporated and the residue treated with water (20 ml) and extracted with dichloromethane. The purification was carried out by flash chromatography eluting with dichloromethane:2N-methanolic-ammonia 96:4 to give 0.17 g of the title compound. Yield 86%.

^{1}H-NMR (CDCl$_3$, δ): 2.17 (s, 1H, NH), 2.31 (s, 3H, CH$_3$), 3.21-3.37 (m, 8H, piperazine CHs), 6.69-6.82 (m, 2H, phenyl CHs), 6.84-6.97 (m, 1H, phenyl CH).

8-{2-[4-(2-Fluoro-5-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method used in Example 3, but using the above intermediate 4A instead of 1-(2-chloro-5-methylphenyl)-piperazine. Purification was carried out by elution with toluene:acetone 93:7. Yield 59%, m.p. 103-104°C.

^{1}H-NMR (CDCl$_3$, δ): 1.24-1.58 (m, 4H, CH$_2$s of spiro ring), 1.59-1.78 (m, 4H, CH$_2$s of spiro ring), 2.28 (s, 3H, CH$_3$), 2.51 (t, 2H, CONCH$_2$CH$_2$N), 2.58 (s, 4H, 2 CH$_2$CO), 2.60-2.77 (m, 4H, piperazine CHs), 2.92-3.09 (m, 4H, piperazine CHs), 3.97 (t, 2H, CONCH$_2$CH$_2$N), 6.62-6.77 (m, 2H, phenyl CHs), 6.78-6.90 (m, 1H, phenyl CH).

Example 5

8-{2-[4-(2,5-Dimethylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method used in Example 3, but using 1-(2,5-dimethylphenyl)-piperazine, instead of 1-(2-chloro-5-methylphenyl)-piperazine. Purification was carried out by elution with toluene:acetone 9:1. Yield 76%, m.p. 128-129°C.

^{1}H-NMR ($CDCl_3$, δ): 1.49-1.62 (m, 4H, CH_2s of spiro ring), 1.68-1.80 (m, 4H, CH_2s of spiro ring), 2.24 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.58 (t, 2H, $CONCH_2\underline{CH_2}N$), 2.60-2.77 (m, 8H, 2 CH_2CO and piperazine CHs), 2.81-2.87 (m, 4H, piperazine CHs), 3.38 (t, 2H, $CON\underline{CH_2}CH_2N$), 6.74-6.83 (m, 2H, phenyl CHs), 7.00-7.09 (m, 1H, phenyl CH).

Example 6

8-{2-[4-(2-Fluoro-5-trifluoromethylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

1-(2-Fluoro-5-trifluoromethyl)-piperazine (6A)

This compound was prepared according to the method described in Example 4 for intermediate 4A, but using 2-fluoro-5-trifluoromethylaniline instead of 2-fluoro-5-methylaniline. Yield 9%.

^{1}H-NMR ($CDCl_3$, δ): 2.08 (s, 1H, NH), 2.89-3.18 (m, 8H, piperazine CHs), 6.95-7.22 (m, 3H, phenyl CHs).

8-{2-[4-(2-Fluoro-5-trifluoromethylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method described in Example 3, but using the above intermediate 6A instead of 1-(2-chloro-5-methylphenyl)-piperazine. Purification was carried out by elution with toluene:acetone 9:1. Yield 81%, m.p. 85-86°C.

^{1}H-NMR ($CDCl_3$, δ): 1.47-1.60 (m, 4H, CH_2s of spiro ring), 1.68-1.79 (m, 4H, CH_2s of spiro ring), 2.57 (t, 2H, $CONCH_2\underline{CH_2}N$), 2.62 (s, 4H, 2 CH_2CO), 2.64-2.78 (m, 4H,

piperazine CHs), 3.04-3.17 (m, 4H, piperazine CHs), 3.95 (t, 2H, CONCH$_2$CH$_2$), 7.00-7.22 (m, 3H, phenyl CHs).

Example 7

8-{2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

1-(5-Chloro-2-methylphenyl)-piperazine (7A)

This compound was prepared according to the method described in Example 4 for intermediate 4A, but using 5-chloro-2-methylaniline instead of 2-fluoro-5-methylaniline. Yield 47%.

^{1}H-NMR (CDCl$_3$, δ): 1.91 (s, 1H, NH), 2.24 (s, 3H, CH$_3$), 2.77-2.95 (m, 4H, piperazine CHs), 2.96-3.09 (m, 4H, piperazine CHs), 6.96 (dd, 2H, phenyl H4 and H6), 7.09 (d, 1H, phenyl H3).

8-[2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethyl]-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method used in Example 3, but using the above intermediate 7A instead of 1-(2-chloro-5-methylphenyl)-piperazine. Purification was carried out eluting with toluene:acetone 9:1. Yield 86%, m.p. 132-133°C. ^{1}H-NMR (CDCl$_3$, δ): 1.46-1.59 (m, 4H, CH$_2$s of spiro ring), 1.59-1.80 (m, 4H, CH$_2$s of spiro ring), 2.21 (s, 3H, CH$_3$), 2.56 (t, 2H, CONCH$_2$CH$_2$N), 2.60-2.72 (m, 8H, 2 CH$_2$CO and piperazine CHs), 2.77-2.96 (m, 4H, piperazine CHs), 3.97 (t, 2H, CONCH$_2$CH$_2$N), 6.87-6.98 (m, 2H, phenyl CHs), 7.00-7.14 (m, 1H, phenyl CH).

Example 8

8-{2-[4-(2,5-Dibromophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

1-(2,5-Dibromophenyl)-piperazine (8A)

This compound was prepared according to the method described in Example 4 for intermediate 4A, but using 2,5-dibromoaniline instead of 2-fluoro-5-methylaniline. Yield 10%.

^{1}H-NMR ($CDCl_3$, δ): 1.89 (s, 1H, NH), 2.92-3.16 (m, 8H, piperazine CHs), 7.02 (dd, 1H, phenyl H4), 7.16 (d, 1H, phenyl H6), 7.22 (d, 1H, phenyl H3).

8-{2-[4-(2,5-Dibromophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method used in Example 3, but using the above intermediate 8A instead of 1-(2-chloro-5-methylphenyl)-piperazine. Purification was carried out eluting with toluene:acetone 92:8. Yield 55%, m.p. 159-160°C.

^{1}H-NMR ($CDCl_3$, δ): 1.43-1.58 (m, 4H, CH_2s of spiro ring), 1.68-1.80 (m, 4H, CH_2s of spiro ring), 2.56 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.61 (s, 4H, 2 CH_2CO), 2.63-2.77 (m, 4H, piperazine CHs), 2.93-3.08 (m, 4H, piperazine CHs), 3.98 (t, 2H, $CONC\underline{H_2}CH_2N$), 7.01 (dd, 1H, phenyl H4), 7.12 (d, 1H, phenyl H6), 7.39 (d, 1H, phenyl H3).

Example 9

8-{2-[4-(5-Chloro-2-cyanophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

1-(5-Chloro-2-cyanophenyl)-piperazine (9A)

This compound was prepared according to the method described in Example 4 for intermediate 4A, but using 2-amino-4-chlorobenzonitrile instead of 2-fluoro-5-methylaniline. Yield 9%.

^{1}H-NMR ($CDCl_3$, δ): 2.77 (s, 1H, NH), 2.91-3.10 (m, 8H, piperazine CHs), 6.58-6.86 (m, 2H, phenyl CHs), 7.19-7.31 (m, 1H, phenyl CH).

8-{2-[4-(5-Chloro-2-cyanophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method used in Example 1, but using the above intermediate 9A instead of 1-(2,5-dichlorophenyl)-piperazine. Yield 23%.
^{1}H-NMR ($CDCl_3$, δ): 1.43-1.60 (m, 4H, CH_2s of spiro ring), 1.63-1.80 (m, 4H, CH_2s of spiro ring), 2.55 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.61 (s, 4H, 2 CH_2CO), 2.63-2.77 (m, 4H, piperazine CHs), 3.11-3.23 (m, 4H, piperazine CHs), 3.96 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.94 (dd, 2H, phenyl CHs), 7.44 (d, 1H, phenyl CH).

Example 10

8-{2-[4-(2-Chloro-5-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

2-Chloro-5-fluoroaniline (10A)

A mixture of 0.17 g (1 mmol) of 2-chloro-5-fluoronitrobenzene, 1.13 g (5 mmol) of tin (II) chloride dihydrate and 10 ml of EtOH was stirred at 70°C for 0.5 hours. After cooling to room temperature, the mixture was poured into H_2O (30 ml), alkalinized with 10% Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give 0.12 g (84.5%) of the desired compound.
^{1}H-NMR ($CDCl_3$, δ): 4.16 (s, 2H, NH_2), 6.51-6.77 (m, 2H, phenyl CHs), 7.09-7.21 (m. 1H, phenyl CH).

1-(2-Chloro-5-fluorophenyl)-piperazine (10B)

This compound was prepared according to the method described in Example 4 for intermediate 4A, but using the above intermediate 10A instead of 2-fluoro-5-methylaniline. Yield 16.5%.
^{1}H-NMR ($CDCl_3$, δ): 2.01 (s, 1H, NH), 2.91-3.10 (m, 8H, piperazine CHs), 6.58-6.76 (m, 2H, phenyl H4 and H6), 7.19-7.31 (m, 1H, phenyl H3).

8-{2-[4-(2-Chloro-5-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method used in Example 1, but using the above intermediate 10B instead of 1-(2,5-dichlorophenyl)-piperazine. Yield 74%, m.p. 139°C.

^{1}H-NMR ($CDCl_3$, δ): 1.43-1.57 (m, 4H, CH_2s of spiro ring), 1.69-1.80 (m, 4H, CH_2s of spiro ring), 2.57 (t, 2H, $CONCH_2\underline{CH_2}N$), 2.60 (s, 4H, 2 CH_2CO), 2.63-2.77 (m, 4H, piperazine CHs), 2.87-3.09 (m, 4H, piperazine CHs), 3.97 (t, 2H, $CON\underline{CH_2}CH_2N$), 6.58-6.80 (m, 2H, phenyl H4 and H6), 7.22-7.31 (m, 1H, phenyl H3).

Example 11

8-{2-[4-(2-Chloro-5-iodophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

1-(2-Chloro-5-iodophenyl)-piperazine (11A)

A solution of 0.32 g (2 mmol) of iodine monochloride in 5 ml of AcOH was added dropwise to a solution of 0.27 g (1 mmol) of 1-(2-chlorophenyl)-piperazine · 2HCl in 5 ml of AcOH. After 2 hours' stirring at room temperature, 5 ml of H_2O was added and the mixture stirred at 80°C for 2 hours. The solvents were evaporated, the residue dissolved in CH_2Cl_2, washed with $Na_2S_2O_3$ then with 10% KOH; the organic layer was dried (Na_2SO_4) and the solvent evaporated to dryness. The crude was purified by flash chromatography eluting with dichloromethane:2N-methanolic-ammonia 96:4 to give 0.032 g (10%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.79 (s, 1H, NH), 2.89-3.11 (m, 8H, piperazine CHs), 6.77 (d, 1H, phenyl H3), 7.49 (dd, 1H, phenyl H4), 7.63 (d, 1H, phenyl H6).

8-{2-[4-(2-Chloro-5-iodophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method used in Example 1, but using the above intermediate 11A instead of 1-(2,5-dichlorophenyl)-piperazine. Yield 73%, m.p. 109-110°C.

^{1}H-NMR ($CDCl_3$, δ): 1.44-1.59 (m, 4H, CH_2s of spiro ring), 1.62-1.79 (m, 4H, CH_2s of spiro ring), 2.54 (t, 2H, $CONCH_2\underline{CH_2}N$), 2.58 (s, 4H, 2 CH_2CO), 2.62-2.77 (m, 4H,

piperazine CHs), 2.83-3.09 (m, 4H, piperazine CHs), 3.97 (t, 2H, CONC$\underline{H}_2$CH$_2$N), 6.77 (d, 1H, phenyl H3), 7.49 (dd, 1H, phenyl H4), 7.64 (d, 1H, phenyl H6).

Example 12

3-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5.5]undecane-2,4-dione

3-(2-Bromoethyl)-3-azaspiro[5.5]undecane-2,4-dione (12A)

A suspension of 4.35 g (24 mmol) of 3-azaspiro[5.5]undecane-2,4-dione and 0.86 g (34.8 mmol) of 80% NaH in 48 ml of DMF was stirred at 60°C for 30 minutes. After cooling to room temperature, it was poured into a solution of 22.2 g (120 mmol) of 1,2-dibromoethane in 152 ml of DMF and the mixture was stirred for 5 hours. The solvent was evaporated in vacuo, the residue was treated with 200 ml of H_2O and extracted with CH_2Cl_2 (3 x 65 ml). The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with cyclohexane:ethyl acetate 7:3 to give 4.1 g (59%) of the desired compound. M.p. 65°C.

^{1}H-NMR (CDCl$_3$, δ): 1.18-1.60 (m, 10H, CH$_2$s azaspiro ring), 2.59 (s, 4H, 2 CH$_2$CO), 3.46 (t, 2H, NCH$_2$), 4.20 (t, 2H, CH$_2$Br).

3-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5.5]undecane-2,4-dione

The title compound was prepared according to the method used in Example 1, but using the above intermediate 12A instead of 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione. Purification was carried out eluting with petroleum ether/ethyl acetate 85:15. Yield 66%.

^{1}H-NMR (CDCl$_3$, δ): 1.37-1.58 (m, 10H, CH$_2$s of spiro ring), 2.56 (s+t, 6H, 2 CH$_2$CO and CONCH$_2$C$\underline{H}_2$N), 2.59-2.73 (m, 4H, piperazine CHs), 2.86-3.04 (m, 4H, piperazine CHs), 3.96 (t, 2H, CONC$\underline{H}_2$CH$_2$N), 6.87 (d, 1H, phenyl H6), 6.96 (dd, 1H, phenyl H4), 7.23 (d, 1H, phenyl H3).

Example 13

1-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-pyrrolidine-2,5-dione

2-[4-(2,5-dichlorophenyl)-1-piperazinyl]-acetonitrile (13A)

A mixture of 0.23 g (1 mmol) of 1-(2,5-dichlorophenyl)-piperazine, 0.15 g (2 mmol) of chloroacetonitrile, 0.21 g (1.5 mmol) of K_2CO_3 and 10 ml of toluene was stirred at reflux for 72 hours. The solvent was evaporated and the residue was treated with 10 ml of H_2O and extracted with ethyl acetate. After solvent evaporation, the crude was purified by flash chromatography eluting with petroleum ether/ethyl acetate 7:3 to give 0.15 g (55%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 2.74-2.87 (m, 4H, piperazine CHs), 3.10-3.22 (m, 4H, piperazine CHs), 3.59 (s, 2H, CH_2CN), 6.97 (dd, 2H, phenyl H4 and H6), 7.28 (d, 1H, phenyl H3).

2-[4-(2,5-dichlorophenyl)-1-piperazinyl]-ethylamine (13B)

A solution of 0.27 g (1 mmol) of the above intermediate 13A in 10 ml of anhydrous Et_2O was added dropwise to a stirred solution of 0.11 g (3 mmol) of lithium aluminium hydride in 10 ml of anhydrous Et_2O kept at 0°C. The mixture was stirred at room temperature for 1.5 hours, then cooled at –10/0°C and treated with 20% NaOH. The inorganic salts were filtered off and washed with CH_2Cl_2. The organic solutions were dried, then evaporated to dryness to give 0.24 g (90%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.48 (m, 2H, NH_2), 2.47 (t, 2H,$C\underline{H_2}NH_2$), 2.56-2.75 (m, 4H, piperazine CHs), 2.78 (t, 2H, $C\underline{H_2}CH_2NH_2$), 2.94-3.16 (m, 4H, piperazine CHs), 6.86 (d, 1H, phenyl H6), 6.96 (dd, 1H, phenyl H4), 7.23 (d, 1H, phenyl H3).

1-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-pyrrolidine-2,5-dione

A solution of 0.1 g (1 mmol) of succinic anhydride, 0.3 g (1.1 mmol) of the above intermediate 13B and 0.02 g of *p*-toluenesulphonic acid in 10 ml of toluene was stirred at reflux for 20 hours. After cooling to room temperature, the solvent was evaporated and the residue purified by flash chromatography eluting with toluene:acetone 9:1 to give 0.23 g (65%) of the title compound. M.p. 122°C.

^{1}H-NMR ($CDCl_3$, δ): 2.58 (t, 2H, $CONCH_2C\underline{H}_2N$), 2.59-2.64 (m, 4H, piperazine CHs), 2.66 (s, 4H, 2 CH_2CO), 2.87-3.09 (m, 4H, piperazine CHs), 3.63 (t, 2H, $CONC\underline{H}_2CH_2N$), 6.86 (d. 1H, phenyl H6), 6.96 (dd, 1H, phenyl H4), 7.22 (d, 1H, phenyl H3).

Example 14

1-{2-[4-(2.5-Dichlorophenyl)-1-piperazinyl]-ethyl}-4-ethyl-4-methylpiperidinyl-2.6-dione

The title compound was prepared according to the method of Example 13, but using 3-ethyl-3-methylglutaric anhydride instead of succinic anhydride. Purification was carried out eluting with toluene:acetone 95:5. Yield 59%; m.p. 98-99°C.

^{1}H-NMR ($CDCl_3$, δ): 0.86 (t, 3H, $C\underline{H}_3CH_2$), 1.03 (s, 3H, CH_3C), 1.40 (q, 2H, $CH_3C\underline{H}_2$), 2.47 (s, 4H, 2 CH_2CO), 2.56 (t, 2H, $CONCH_2C\underline{H}_2N$), 2.59-2.73 (m, 4H, piperazine CHs), 2.83-3.10 (m, 4H, piperazine CHs), 3.94 (t, 2H, $CONC\underline{H}_2CH_2N$), 6.88 (d, 1H, phenyl H6), 6.95 (dd, 1H, phenyl H4), 7.21 (d, 1H, phenyl H3).

Example 15

2-{2-[4-(2.5-Dichlorophenyl)-1-piperazinyl]-ethyl}-2-azaspiro[4.4]nonane-1.3-dione

Ethyl cyclopentanecarboxylate (15A)

0.15 g (1.2 mmol) of oxalyl chloride was added dropwise at 0°C to a stirred solution of 0.11 g (1 mmol) of cyclopentanecarboxylic acid in 10 ml of CH_2Cl_2 and 2 drops of DMF. The solution was then stirred at room temperature for 4 hours. The solvent was evaporated off, the residue dissolved in 10 ml of CH_2Cl_2 and this solution was added dropwise at 0°C to 10 ml of ethanol. After 20 hours' stirring at room temperature, the solvents were evaporated to dryness and the residue purified by flash chromatography eluting with petroleum ether:ethyl acetate 98:2 to give 0.042 g (32%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.27 (t, 3H, $CH_2C\underline{H}_3$), 1.44-1.98 (m, 8H, cyclopentane CH_2s), 2.61-2.82 (m, 1H, CH), 4.11 (q, 2H, $C\underline{H}_2CH_3$).

Ethyl (1-ethoxycarbonyl-1-cyclopentyl)-acetate (15B)

0.4 ml (1 mmol) of 2.5 M *n*-butyl lithium in THF was added dropwise to a solution of 0.1 g (1 mmol) of diisopropylamine in 10 ml of anhydrous THF stirred at –70°C under a N_2 atmosphere. After 30 minutes stirring, a solution of 0.14 g (1 mmol) of the above intermediate 15A in 5 ml of anhydrous THF was added and stirring was continued for 1 hour, then a solution of 0.17 g (1 mmol) of ethyl bromoacetate in 5 ml of anhydrous THF was added. After 1 hour stirring at –70°C, the mixture was heated at room temperature and stirred for 20 hours, then a solution of 0.43 g of NH_4Cl in 20 ml of H_2O was added and the mixture extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate 95:5 to give 0.044 g (19%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.21 (t, 6H, $CH_2C\underline{H_3}$), 1.44-1.93 (m, 6H, cyclopentyl CHs), 2.02-2.21 (m, 2H, cyclopentyl CHs), 2.67 (s, 2H, CH_2CO), 4.11 (q, 4H, $C\underline{H_2}CH_3$).

2-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-2-azaspiro[4.4]nonane-1,3-dione

A mixture of 0.11 g (0.48 mmol) of the above intermediate 15B, 0.23 g (0.84 mmol) of intermediate 13B was heated overnight at 120°C in an autoclave. After cooling to room temperature, the crude was purified by flash chromatography eluting with toluene:acetone 9:1 to give 0.03 g (15%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 1.60-1.82 (m, 4H, CH_2s of spiro ring), 1.83-2.24 (m, 4H, CH_2s of spiro ring), 2.57 (s, 2H, CH_2CO), 2.62-2.75 (m, 6H, $CONCH_2C\underline{H_2}N$ and piperazine CHs), 2.93-3.09 (m, 4H, piperazine CHs), 3.68 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.96 (dd, 2H, phenyl H4 and H6), 7.23 (d, 1H, phenyl H3).

Example 16

7-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-7-azaspiro[3.5]nonane-6,8-dione

A solution of 0.13 g (0.75 mmol) of cyclobutane-1,1-diacetic acid, prepared as described in *Bull. Soc. Chim. Fr.* 2572-2581 (1964), and 0.17 g (0.83 mmol) of

dicyclohexylcarbodiimide in 5 ml of anhydrous DMF was stirred at room temperature for 1.5 hours. Then a solution of 0.21 g (0.79 mmol) of intermediate 13B in 1 ml of anhydrous DMF was added and the mixture stirred for 18 hours. The precipitate was separated by filtration and the solvent evaporated to dryness. 0.18 g (2.26 mmol) of sodium acetate and 5 ml of acetic anhydride were added to the residue and the resulting mixture was heated at 100°C for 2 hours. After cooling to room temperature, the suspension was poured into 10 ml of iced H_2O, stirred for 30 min, alkalinized with 2.5 N NaOH, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with toluene:acetone 8:2 to give 0.09 g (29%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 1.84-2.06 (m, 6H, CH_2s of spiro ring), 2.51 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.57-2.68 (m, 4H, piperazine CHs), 2.73 (s, 4H, 2 CH_2CO), 2.87-3.09 (m, 4H, piperazine CHs), 3.94 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.88 (dd, 1H, phenyl H4), 6.96 (d, 1H, phenyl H6), 7.23 (d, 1H, phenyl H3).

Example 17

<u>8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-1-methylethyl}-8-azaspiro[4.5]decane-7,9-dione</u>

<u>8-(2-Chloro-1-methylethyl)-8-azaspiro[4.5]decane-7,9-dione (17A)</u>

A solution of 0.17 g (1 mmol) of diethyl azodicarboxylate in 1 ml of DMF was added dropwise to a solution of 0.17 g (1 mmol) of 8-azaspiro[4.5]decane-7,9-dione, 0.19 g (2 mmol) of 1-chloro-2-propanol and 0.26 g (1 mmol) of triphenylphosphine in 3 ml of DMF, and the mixture was stirred at 35°C for 72 hours. After cooling to room temperature, 20 ml of H_2O was added and the mixture extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate 9:1 to give 0.067 g (28%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.29-1.41 (m, 3H, CH_3), 1.42-1.58 (m, 4H, CH_2s of spiro ring), 1.60-1.78 (m, 4H, CH_2s of spiro ring), 2.57 (s, 4H, 2 CH_2CO), 3.57-3.88 (m, 1H, C<u>H</u>(H)Cl), 4.03-4.19 (m, 1H, CH(<u>H</u>)Cl), 4.96-5.13 (m, 1H, NCH).

<u>8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-1-methylethyl}-8-azaspiro[4.5]decane-7,9-dione</u>

The title compound was prepared according to the method of Example 1, but using the above intermediate 17A instead of 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione. Heating lasted 45 minutes and purification was carried out eluting with toluene/acetone 95:5. Yield 21%.

^{1}H-NMR ($CDCl_3$, δ): 1.34 (d, 3H, CH_3), 1.51-1.61 (m, 4H, CH_2s of spiro ring), 1.62-1.80 (m, 4H, CH_2s of spiro ring), 2.31-2.43 (m, 1H, $CH(CH_3)C\underline{H}(H)N$), 2.44-2.55 (m, 2H, piperazine CHs), 2.58 (s, 4H, 2 CH_2CO), 2.62-2.77 (m, 2H, piperazine CHs), 2.85-3.05 (m, 4H, piperazine CHs), 3.06-3.22 (m, 1H, $CH(CH_3)CH(\underline{H})N$), 4.95-5.12 (m, 1H, NCH), 6.93 (dd, 2H, phenyl H4 and H6), 7.22 (d, 1H, phenyl H3).

Example 18

<u>8-{2-[4-(2,5-Dichlorophenyl)-1-piperidinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione</u>

<u>Diethyl 2,5-dichlorobenzylidenemalonate (18A)</u>

A mixture of 0.17 g (1 mmol) of 2,5-dichlorobenzaldehyde, 0.32 g (2 mmol) of diethyl malonate and 0.66 g (5 mmol) of $AlCl_3$ was stirred at room temperature for 4 hours, then poured into ice-water mixture. 37% HCl was then added and the mixture extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated, and the residue purified by flash chromatography eluting with petroleum ether/ethyl acetate 9:1 to give 0.16 g (51%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.24 (t, 3H, $CH_2C\underline{H}_3$), 1.37 (t, 3H, $CH_2C\underline{H}_3$), 4.31 (q, 4H, 2 $C\underline{H}_2CH_3$), 7.24 (dd, 2H, phenyl H3 and H4), 7.41 (d, 1H, phenyl H6), 7.94 (s, 1H, CH).

<u>Diethyl 3-(2,5-dichlorophenyl)-2,4-diethoxycarbonylglutarate (18B)</u>

A mixture of 0.31 g (1 mmol) of the above intermediate 18A, 0.16 g (1 mmol) of diethyl malonate and 0.4 g (3 mmol) of $AlCl_3$ was heated at 60°C for 6 hours. Isolation of the crude and its purification was carried out as for intermediate 18A and gave 0.16 g (34%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.07 (t, 6H, 2 $CH_2C\underline{H}_3$), 1.22 (t, 6H, 2 $CH_2C\underline{H}_3$), 4.01 (q, 4H, 2 $C\underline{H}_2CH_3$), 4.12 (q, 6H, 2 $C\underline{H}_2CH_3$ and 2 CHCO), 4.68-4.86 (m, 1H, CHC$\underline{H}$CH), 7.10 (dd, 1H, phenyl H4), 7.22 (d, 1H, phenyl H3), 7.46 (d, 1H, phenyl H6).

<u>3-(2.5-Dichlorophenyl)-glutaric acid (18C)</u>

A mixture of 0.48 g (1 mmol) of the above intermediate 18B and 5 ml of 47% HBr was heated at reflux for 48 hours. After cooling to room temperature, the precipitate was collected by suction and dried to give 0.2 g (73%) of the desired compound.

^{1}H-NMR (DMSO-d_6, δ): 2.40 (t, 4H, 2 CH_2COO), 3.96 (q, 1H, CH), 7.31 (dd, 1H, phenyl H4), 7.49 (d, 1H, phenyl H3), 7.57 (d, 1H, phenyl H6), 12.50 (s, 2H, 2 COOH).

<u>1-Cyanomethyl-4-(2.5-dichlorophenyl)-piperidine-2,6-dione (18D)</u>

A solution of 0.28 g (1 mmol) of the above intermediate 18C and 0.23 g (1.1 mmol) of N,N'-dicyclohexylcarbodiimide in 5 ml of anhydrous DMF was stirred at room temperature for 1.5 hours, then 0.22 g (1.05 mmol) of aminoacetonitrile and 0.11 g (1.05 mmol) of triethylamine were added. The mixture was stirred at room temperature for 18 hours, then the precipitate was filtered off and the solvent evaporated under vacuum. 0.25 g (3 mmol) of sodium acetate and 5 ml of acetic anhydride were added to the residue and the mixture was heated at 100°C for 2 hours. After cooling to room temperature, the suspension was poured into 10 ml of ice water, stirred for 30 minutes, alkalinized with 2.5 N NaOH and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with petroleum ether/ethyl acetate 85:15 to give 0.14 g (47%) of the desired compound.

[1]H-NMR ($CDCl_3$, δ): 2.72-2.96 (m, 2H, CH_2CO), 3.01-3.22 (m, 2H, CH_2CO), 3.71 (s, 2H, CH_2CN), 3.73-3.97 (m, 1H, CH), 7.24 (dd, 1H, phenyl H4), 7.38 (d, 1H, phenyl H3), 7.67 (d, 1H, phenyl H6).

2-[4-(2,5-dichlorophenyl)-1-piperidinyl]-ethylamine (18E)

A solution of 0.3 g (1 mmol) of the above intermediate 18D in 5 ml of anhydrous Et_2O was added dropwise to a solution of 0.15 g (4 mmol) of $LiAlH_4$ in 5 ml of anhydrous Et_2O maintaining a gentle reflux. The mixture was stirred at reflux for 2 hours, then rested overnight at room temperature. The mixture was cooled at –10/0°C and the excess of $LiAlH_4$ was neutralised by 20% NaOH addition. The inorganic salts were filtered and washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with CH_2Cl_2:2N-methanolic-ammonia 98:2 to give 0.1 g (37%) of the desired compound.

[1]H-NMR ($CDCl_3$, δ): 1.77-1.96 (m, 4H, 2 piperidine CHs and NH_2), 1.97-2.28 (m, 2H, piperidine CHs), 2.42-2.56 (m, 2H, $N\underline{CH_2}CH_2NH_2$), 2.77-2.94 (m, 5H, piperidine CHs and $NCH_2\underline{CH_2}NH_2$), 2.96-3.21 (m, 2H, piperidine CHs), 7.08-7.37 (m, 3H, phenyl CHs).

8-{2-[4-(2,5-Dichlorophenyl)-1-piperidinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method of Example 13, but using the above intermediate 18E instead of intermediate 13B and 3,3-tetramethyleneglutaric acid instead of succinic anhydride. Yield 27%.

[1]H-NMR ($CDCl_3$, δ): 1.45-1.63 (m, 4H, CH_2s of spiro ring), 1.64-1.97 (m, 8H, CH_2s of spiro ring and 4 piperidine CHs), 2.07-2.23 (m, 2H, piperidine CHs), 2.50 (t, 2H, $CONCH_2\underline{CH_2}N$), 2.64 (s, 4H, 2 CH_2CO), 2.83-3.16 (m, 3H, piperidine CHs), 4.38 (t, 2H, $CON\underline{CH_2}CH_2N$), 7.01-7.24 (m, 3H, phenyl CHs).

Example 19

N-(2,5-Dichlorophenyl)-N'-{2-(7,9-dioxo-8-azaspiro[4.5]decane-8-yl)-ethyl}-N,N'-dimethyl-1,2-diaminoethane

N-(2.5-Dichlorophenyl)-2-aminoethanol (19A)

A mixture of 0.16 g (1 mmol) of 2,5-dichloroaniline, 0.8 g (10 mmol) of 2-chloroethanol and 0.15 g (1.5 mmol) of triethylamine was stirred at 150°C for 16 hours. The crude was purified by flash chromatography eluting with cyclohexane:ethyl acetate 7:3 to give 0.09 g (45%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.59-1.88 (m, 1H, NH), 3.36 (t, 2H, NCH_2), 3.93 (t, 2H, CH_2O), 4.57-4.84 (m, 1H, OH), 6.63 (dd, 2H, phenyl H4 and H6), 7.17 (d, 1H, phenyl H3).

N-(2.5-Dichlorophenyl)-2-methylamino-ethanol (19B)

A mixture of 0.21 g (1 mmol) of the above intermediate 19A, 0.083 ml (3 mmol) of 37% HCHO and 0.14 g (3 mmol) of formic acid was heated at reflux for 18 h. After cooling to room temperature, concentrated HCl was added until pH 1, the solvent evaporated to dryness, the residue alkalinized with 2 N NaOH, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with petroleum ether:ethyl acetate 8:2 to give 0.05 g (23%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 2.49-2.63 (m, 1H, OH), 2.77 (s, 3H, CH_3), 3.17 (t, 2H, NCH_2), 3.74 (t, 2H, CH_2O), 6.96 (dd, 2H, phenyl H4 and H6), 7.27 (d, 1H, phenyl H3).

N-(2.5-Dichlorophenyl)-N-methyl-2-chloroethylamine (19C)

0.14 g (1.2 mmol) of thionyl chloride was added to a solution of 0.22 g (1 mmol) of the above intermediate 19B in 10 ml of CH_2Cl_2 containing 3 drops of DMF stirred at 0°C, and the mixture was stirred for 0.5 hours at room temperature and at reflux for 3 hours. The solvent was evaporated and the crude suspended in CH_2Cl_2 and re-evaporated. The residue was alkalinized with 2 N NaOH and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give 0.19 g (83%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 2.85 (s, 3H, CH_3), 3.40 (t, 2H, NCH_2), 3.68 (t, 2H, CH_2Cl), 6.97 (dd, 1H, phenyl H4), 7.06 (d, 1H, phenyl H6), 7.24 (d, 1H, phenyl H3).

N,N'-Dimethyl-N-(2,5-dichlorophenyl)-ethylenediamine (19D)

A mixture of 0.24 g (1 mmol) of the above intermediate 19C and 4.32 ml (8.65 mmol) of 2 N methanolic methylamine solution was heated at 60-80°C for 20 hours in an autoclave. After cooling to room temperature, the solvent was evaporated and the residue was purified by flash chromatography eluting with dichloromethane:2N-methanolic-ammonia 96:4 to give 0.067 g (29%) of the desired compound.

^{1}H-NMR ($CDCl_3$, δ): 1.93-2.02 (m, 1H, NH), 2.46 (s, 3H, CH_3), 2.77 (t+s, 5H, CH_2N and CH_3), 3.17 (t, 2H, NCH_2), 6.97 (dd, 1H, phenyl H4), 7.06 (d, 1H, phenyl H6), 7.24 (d, 1H, phenyl H3).

N-(2,5-dichlorophenyl)-N'-{2-(7,9-dioxo-8-azaspiro[4.5]decane-8-yl)-ethyl}-N,N'-dimethyl-1,2-diaminoethane

The title compound was prepared according to the method used in Example 1, but using the above intermediate 19D instead of 1-(2,5-dichlorophenyl)-piperazine and heating at 140°C. Purification was carried out eluting with toluene/methanol 95:5. The residue was dissolved in dichloromethane, the solution acidified by ethereal HCl addition. The filtered hydrochloride salt was dissolved in dichloromethane, and the mixture made alkaline by NaOH addition. The organic layer was dried (Na_2SO_4) and evaporated to dryness to give the title compound. Yield 18%.

^{1}H-NMR ($CDCl_3$, δ): 1.43-1.59 (m, 4H, CH_2s of spiro ring), 1.61-1.79 (m, 4H, CH_2s of spiro ring), 2.36 (s, 3H, NCH_3), 2.44-2.73 (m, 8H, 2 CH_2CO and $CONCH_2\underline{CH_2}N(CH_3)\underline{CH_2}$), 2.82 (s, 3H, NCH_3), 3.09-3.18 (m, 2H, $C\underline{H_2}N(CH_3)Ar$), 3.88 (t, 2H, $CONC\underline{H_2}CH_2$), 6.90 (dd, 1H, phenyl H4), 7.01 (d, 1H, phenyl H6), 7.24 (d, 1H, phenyl H3).

Example 20

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one

Methyl (1-formylmethyl-1-cyclopentyl)-acetate (20A)

0.7 g (5.5 mmol) of oxalyl chloride was dropped into a solution of 1 g (5 mmol) of 1,1-cyclopentanediacetic acid monomethyl ester, prepared as described in *J. Chem. Soc.* 713-721 (1929), in 20 ml of CH_2Cl_2 containing some drops of DMF, at 10-15°C. After 2 hours' stirring at room temperature the solvent was evaporated to dryness. The residue was dissolved in 20 ml of acetone and this solution was added to a mixture of 2 ml of diisopropylethylamine and 0.1 g of 10% Pd/C in 20 ml of anhydrous acetone previously stirred in hydrogen atmosphere. The mixture was hydrogenated at normal pressure until one equivalent of hydrogen was adsorbed, then the catalyst was filtered off and the solvent evaporated to dryness. The residue was purified by flash chromatography eluting with cyclohexane:ethyl acetate 9:1 to give 0.63 g (69%) of the desired compound.
^{1}H-NMR ($CDCl_3$), δ): 1.39-1.63 (m, 8H, cyclopentyl CH_2s), 2.41 (s, 2H, CH_2COO), 2.58 (m, 2H, $C\underline{H_2}CHO$), 3.57 (s, 3H, CH_3), 9.61-9.75 (m, 1H, CHO).

<u>8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one</u>

0.009 g (0.29 mmol) of $NaBH_4$ was added to a stirred solution of 0.092 g (0.5 mmol) of the above intermediate 20A and 0.16 g (0.58 mmol) of intermediate 13B in 10 ml of MeOH, at 0°C. After 1.5 hours' stirring, the solvent was evaporated, the residue treated with 5 ml of H_2O and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography eluting with toluene/acetone 75:25 to give 0.14 g (68%) of the title compound. M.p. 88-89°C.
^{1}H-NMR ($CDCl_3$, δ): 1.19-1.58 (m, 4H, CH_2s of spiro ring), 1.59-1.80 (m, 6H, CH_2s of spiro ring and $CC\underline{H_2}CH_2N$), 2.27 (s, 2H, CH_2CO), 2.59 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.62-2.78 (m, 4H, piperazine CHs), 2.97-3.17 (m, 4H, piperazine CHs), 3.21 (t, 2H, $CCH_2C\underline{H_2}N$), 3.57 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.88-7.02 (m, 2H, phenyl CHs), 7.22-7.32 (m, 1H, phenyl CH).
The monohydrochloride was also prepared, m.p. > 230°C (EtOH).

Example 21

<u>8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]dec-9,10-en-7-one</u>

A mixture of 0.08 g (0.44 mmol) of intermediate 20A, 0.14 g (0.51 mmol) of intermediate 13B, 0.02 g of *p*-toluenesulphonic acid and 10 ml of toluene was stirred at reflux overnight distilling off the azeotrope. After cooling to room temperature, the solvent was evaporated to dryness and the residue purified by flash chromatography eluting with toluene:acetone 9:1 to give 0.09 g (51%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 1.43-1.59 (m, 4H, CH_2s of spiro ring), 1.61-1.77 (m, 4H, CH_2s of spiro ring), 2.38 (s, 2H, CH_2CO), 2.58 (t, 2H, $CONCH_2\underline{CH_2}$), 2.60-2.98 (m, 4H, piperazine CHs), 2.96-3.15 (m, 4H, piperazine CHs), 3.61 (t, 2H, $CON\underline{CH_2}CH_2$), 5.09 (d, 1H, H10), 5.96 (d, 1H, H9), 6.86-7.03 (m, 2H, phenyl CHs), 7.20-7.27 (m, 1H, phenyl CH).

Example 22

<u>8-{2-[4-(2.5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane</u>

0.2 ml (1.62 mmol) of boron trifluoride etherate was added to a suspension of 0.15 g (0.33 mmol) of the compound from Example 20, 0.05 g (1.32 mmol) of $NaBH_4$ in 10 ml of THF stirred at 0°C in nitrogen atmosphere. The mixture was stirred at room temperature for 4 hours and at 60°C for 5 hours. 4 ml of 2N HCl was then added, the solvent evaporated and the residue alkalinized with 1N NaOH up to pH 8. The mixture was extracted with dichloromethane (3 x 10 ml), the organic phase dried (Na_2SO_4) and the solvent evaporated to dryness. The residue was purified by flash chromatography eluting with toluene:acetone 95:5 to give 0.068 g of a crude which was heated at reflux for 2 hours in 10 ml of methanol and 0.5 ml of 2N HCl. After cooling to 20-25°C, the solvents were evaporated to dryness, the residue was alkalinized with 1N NaOH and extracted with dichloromethane (3 x 10 ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness to give 0.058 g (44%) of the title compound as an oil.

^{1}H-NMR ($CDCl_3$, δ): 1.32-1.46 (m, 4H, CH_2s of spiro ring), 1,47-1,54 (m, 4H, CH_2s of spiro ring), 1.57-1.68 (m, 4H, CH_2s of spiro ring), 2.38-2.50 (m, 4H, CH_2s of spiro ring and CH_2s of ethyl chain), 2.51-2.63 (m, 4H, CH_2s of spiro ring and CH_2s of ethyl chain), 2.64-2.77 (m, 4H, piperazine CHs), 3.00-3.12 (m, 4H, piperazine CHs), 6.91 (d, 1H, phenyl CH), 6.99 (dd, 1H, phenyl CH), 7.27 (d, 1H, phenyl CH).

Example 23

8-{2-[4-(2-Chloro-5-nitrophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

1-(2-Chloro-5-nitrophenyl)-piperazine (23A)

The title compound was prepared according to the method described in Example 4 for intermediate 4A, but using 2-chloro-5-nitroaniline instead of 2-fluoro-5-methylaniline. Yield 6%.

^{1}H-NMR ($CDCl_3$, δ): 2.58 (s, 1H, NH), 2.92-3.14 (m, 8H, piperazine CHs), 7.42 (d, 1H, phenyl H3), 7.76 (dd, 2H, phenyl H4 and H6).

8-{2-[4-(2-Chloro-5-nitrophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

The title compound was prepared according to the method described in Example 4, but using the above intermediate 23A instead of intermediate 4A. Yield 31%; m.p. 116-117°C.

^{1}H-NMR ($CDCl_3$, δ): 1.46-1.61 (m, 4H, CH_2s of spiro ring), 1.62-1.79 (m, 4H, CH_2s of spiro ring), 2.57 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.59 (s, 4H, 2 CH_2CO), 2.64-2.77 (m, 4H, piperazine CHs), 2.98-3.17 (m, 4H, piperazine CHs), 3.97 (t, 2H, $CONC\underline{H_2}CH_2N$), 7.24 (d, 1H, phenyl H3), 7.78 (dd, 2H, phenyl H4 and H6).

Example 24

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one N^1-oxide

A solution of 0.3 g (0.615 mmol) of magnesium monoperoxyphthalate hexahydrate in 4 ml of H_2O was dropped at 10-15°C to a stirred solution of 0.5 g (1.23 mmol) of the compound of Example 20 in 10 ml of methanol and 10 ml of chloroform. The mixture was stirred at 20-25°C for 4 hours then the solvent was evaporated to dryness. The residue was treated with 10 ml of H_2O, alkalinized with a 20% sodium carbonate aqueous solution until pH 8 and extracted with dichloromethane (3 x 5 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified

by flash chromatography eluting with dichloromethane:methanol 9:1 to afford 0.41 g (78%) of the title compound. M.p. 153.9-154.3°C.

^{1}H-NMR ($CDCl_3$, δ): 1.40-1.59 (m, 4H, CH_2s of spiro ring), 1.60-1.82 (m, 6H, CH_2s of spiro ring), 2.25 (s, 2H, CH_2CO), 3.20-3.35 (m, 2H, piperazine CHs), 3.49-3.62 (m, 4H, piperazine CHs), 3.62-3.79 (m, 6H, CONC$\underline{H}_2$$CH_2C, CONCH_2C\underline{H}_2$N and 2 piperazine CHs), 3.90-4.06 (m, 2H, CONC$\underline{H}_2$$CH_2$N), 7.06 (dd, 2H, phenyl CHs), 7.31 (d, 1H, phenyl CH).

Example 25

8-{2-[4-(2,4,5-Trifluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one

1-(2,4,5-Trifluorophenyl)-piperazine (25A)

A mixture of 0.74 g (5mmol) of 2,4,5-trifluoroaniline, 0.91 g (5 mmol) of *bis*-(2-chloroethyl)amine hydrochloride, 2.5 ml of o-dichlorobenzene, and 0.25 ml of n-hexanol was stirred at reflux temperature for 7.5 hours. After cooling to room temperature, the mixture was treated with 2N NaOH (10 ml) and extracted with diethyl ether (3 x 20 ml). Purification was carried out by flash chromatography eluting with dichloromethane:2N methanolic ammonia gradient from 100:5 to 100:10 to give 0.65 g of the title compound. Yield: 60%.

^{1}H-NMR ($CDCl_3$, δ): 2.97-3.18 (m, 8H, piperazine CHs), 3.32 (s, 1H, NH); 6.68-7.00 (m, 2H, phenyl CHs).

2-[4-(2,4,5-trifluorophenyl)-1-piperazinyl]-acetonitrile (25B)

This compound was prepared according to the method of Example 13 for compound 13A, but using the above intermediate 27A instead of 1-(2,5-dichlorophenyl)-piperazine, and the mixture was stirred at 140°C for 5 hours. Yield 59%.

^{1}H-NMR ($CDCl_3$, δ): 2.72-2.86 (m, 4H, piperazine CHs), 3.05-3.19 (m, 4H, piperazine CHs), 3.56 (s, 2H, CH_2CN), 6.69-6.81 (m, 1H, phenyl CH), 6.82-7.01 (m, 1H, phenyl CH).

2-[4-(2.4.5-trifluorophenyl)-1-piperazinyl]-ethylamine (25C)

This compound was prepared according to the method of Example 13 for compound 13B, but using the above intermediate 25B instead of intermediate 13A. Yield 93%.

^{1}H-NMR ($CDCl_3$, δ): 1.50 (s, 2H, NH_2), 2.51 (t, 2H, CH_2NH_2), 2.56-2.74 (m, 4H, piperazine CHs), 2.83 (t, 2H, $CH_2CH_2NH_2$), 2.96-3.17 (m, 4H, piperazine CHs), 6.68-7.01 (m, 2H, phenyl CHs).

8-{2-[4-(2.4.5-Trifluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one

The title compound was prepared according to the method of Example 20, but using the above intermediate 27C instead of intermediate 13B. Yield 74%; m.p. 98.5-99°C.

^{1}H-NMR ($CDCl_3$, δ): 1.41-1.57 (m, 4H, CH_2s of spiro ring), 1.58-1.79 (m, 6H, CH_2s of spiro ring), 2.37 (s, 2H, CH_2CO), 2.61 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.63-2.79 (m, 4H, piperazine CHs), 2.96-3.12 (m, 4H, piperazine CHs), 3.41 (t, 2H, $CONC\underline{H_2}CH_2C$), 3.56 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.68-7.01 (m, 2H, phenyl CHs).

Example 26

3-{2-[4-(2.5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5.5]undecane-2-one

Methyl (1-formylmethyl-1-cyclohexyl)-acetate (26A)

This compound was prepared according to the method of Example 20 for compound 20A, but using 1,1-cyclohexanediacetic acid monomethyl ester, prepared as described in *J. Chem. Soc.* 713-721 (1929), instead of 1,1-cyclopentanediacetic acid monomethyl ester. Purification was carried out by flash chromatography eluting with petroleum ether:ethyl acetate 95:5. Yield 39%.

^{1}H-NMR ($CDCl_3$, δ): 1.38-1.59 (m, 10H, cyclohexane CH_2s), 2.51 (s, 2H, CH_2COOCH_3), 2.59 (d, 2H, CH_2CHO), 3.66 (s, 3H, $COOCH_3$), 9.87 (t, 1H, CHO).

3-{2-[4-(2.5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5.5]undecane-2-one

The title compound was prepared according to the method of Example 20, but using the above intermediate 26A instead of 20A. Purification was carried out by flash chromatography eluting with toluene:acetone 8:2. Yield 51%; m.p. 65.5-66°C.

^{1}H-NMR ($CDCl_3$, δ): 1.32-1.55 (m, 10H, CH_2s of spiro ring), 1.70 (t, 2H, $CONCH_2CH_2C$), 2.25 (s, 2H, CH_2CO), 2.58-2.75 (m, 6H, piperazine CHs and $CONCH_2CH_2N$), 2.97-3.10 (m, 4H, piperazine CHs), 3.38 (t, 2H, $CONCH_2CH_2C$), 3.52 (t, 2H, $CONCH_2CH_2N$), 6.89-7.00 (m, 2H, phenyl CHs), 7.25 (d, 1H, phenyl CH).

Example 27

3-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5,6]dodecane-2,4-dione.

The title compound was prepared according to the method of Example 16, using cycloheptane-1,1-diacetic acid, prepared as described in *Indian J. Chem.* 1, 256-258 (1963), instead of cyclobutane-1,1-diacetic acid. The residue was purified by flash chromatography eluting with toluene:acetone 95:5. Yield 36%.

^{1}H-NMR ($CDCl_3$, δ): 1.36-1.61 (m, 12H, CH_2s of spiro ring), 2.51-2.61 (m, 6H, 2 CH_2CO and $CONCH_2\underline{CH_2}N$), 2.63-2.74 (m, 4H, piperazine CHs), 2.89-3.08 (m, 4H, piperazine CHs), 3.97 (t, 2H, $CON\underline{CH_2}CH_2N$), 6.96 (dd, 2H, phenyl CHs), 7.27 (d, 1H, phenyl CHs).

Example 28

8-{2-[4-(5-Chloro-2-cyanophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one

8-(2-Hydroxyethyl)-8-azaspiro[4.5]decane-7-one (28A)

To a solution of 1.1 g (6 mmol) of intermediate 20A and 0.42 ml (7.02 mmol) of 2-aminoethanol, cooled at 0°C, 0.11 g (3 mmol) of $NaBH_4$ was added and the resulting mixture stirred at 20-25°C for 45 minutes. The solvent was evaporated to dryness at reduced pressure, H_2O (25 ml) was added and the solution extracted with CH_2Cl_2 (3x20 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated *in vacuo*. The crude was purified by flash chromatography eluting with ethyl acetate:methanol 95:5 to give 0.87 g (76%) of the title compound as an oil.

[1]H-NMR ($CDCl_3$, δ): 1.41-1.59 (m, 4H, CH_2s of spiro ring), 1.61-1.72 (m, 4H, CH_2s of spiro ring), 1.74 (t, 2H, $CONCH_2C\underline{H_2}C$), 2.31 (s, 2H, CH_2CO), 2.60 (bs, 1H, OH), 3.02 (t, 2H, $CONC\underline{H_2}CH_2OH$), 3.39 (t, 2H, $CONC\underline{H_2}CH_2C$), 3.79 (t, 2H, $CONCH_2C\underline{H_2}OH$).

8-(2-Chloroethyl)-8-azaspiro[4.5]decane-7-one (28B)

To a solution of 0.28 g (1.4 mmol) of the above intermediate 28A in 10 ml of CH_2Cl_2 cooled at 0°C, a solution of 0.12 ml (1.69 mmol) of $SOCl_2$ in 2 ml of CH_2Cl_2 and DMF (5 drops) was added and the mixture stirred at 20-25°C for 30 minutes, then refluxed for 3 hours. After cooling to room temperature, the solvent was evaporated to dryness. CH_2Cl_2 (20 ml) was added and evaporated. The crude was alkalinized with 1 N NaOH (pH=8) and extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness under vacuum to give 0.29 g (95%) of the desired compound as an oil.

[1]H-NMR ($CDCl_3$, δ): 1.38-1.53 (m, 4H, CH_2s of spiro ring), 1.61-1.74 (m, 4H, CH_2s of spiro ring), 1.75 (t, 2H, $CONCH_2C\underline{H_2}C$), 2.32 (s, 2H, CH_2CO), 3.47 (t, 2H, $CONC\underline{H_2}CH_2C$), 3.61-3.79 (m, 4H, $C\underline{H_2}C\underline{H_2}Cl$).

8-{2-[4-(5-Chloro-2-cyanophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one

The title compound was prepared according to the method used in Example 1, but using intermediate 9A instead of 1-(2,5-dichlorophenyl)-piperazine and the above intermediate 28B instead of 8-(2-bromoethyl)-8-azaspiro[4.5]decane-7,9-dione. The crude was purified by flash chromatography eluting with petroleum ether/ethyl acetate gradient from 2:8 to 0:10. Yield 33% of the title compound as an oil.

[1]H-NMR ($CDCl_3$, δ): 1.39-1.51 (m, 4H, CH_2s of spiro ring), 1.54-1.72 (m, 4H, CH_2s of spiro ring), 1.75 (t, 2H, $CONCH_2C\underline{H_2}C$), 2.24 (s, 2H, CH_2CO), 2.69 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.70-2.88 (m, 4H, piperazine CHs), 3.21-3.32 (m, 4H, piperazine CHs), 3.39 (t, 2H, $CONC\underline{H_2}CH_2C$), 3.54 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.97 (dd, 2H, phenyl H4 and H6), 7.48 (dd, 1H, phenyl H3).

Example 29

8-{2-[4-(5-Chloro-2-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione

1-(5-Chloro-2-fluorophenyl)-piperazine (29A)

A mixture of 1 g (6.87 mmol) of 5-chloro-2-fluoroaniline, 1.35 g (7.55 mmol) of *bis*-(2-chloroethyl)-amine hydrochloride, 3 ml of *o*-dichlorobenzene and 0.3 ml of *n*-hexanol was stirred at reflux temperature for 11 h. After cooling to room temperature, the mixture was treated with 10 ml of 2 N NaOH and extracted with CH_2Cl_2 (3x20 ml). The combined organic layers were washed with H_2O, dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The purification was carried out by flash chromatography eluting with CH_2Cl_2 : 2 N methanolic ammonia 97:3 to give 1.13 g (76.6%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 2.06 (bs, 1H, NH), 3.01-3.12 (m, 8H, piperazine CHs), 6.86-7.03 (m, 3H, phenyl CHs).

N-{2-[4-(5-Chloro-2-fluorophenyl)-1-piperazinyl]-ethyl}-phthalimide (29B)

A mixture of 1.13 g (5.26 mmol) of the above intermediate 29A, 1.31 g (5.16 mmol) of 1-(2-bromoethyl)-phthalimide and 1.82 g (13.15 mmol) of K_2CO_3 in 20 ml of CH_3CN was stirred under N_2 atmosphere at 20-25°C for 6 h, then at 50-60°C for 9 h. After cooling to room temperature, the solvent was evaporated at reduced pressure. H_2O (20 ml) was added and the mixture extracted with CH_2Cl_2 (3x15 ml). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The crude was purified by flash chromatography eluting with CH_2Cl_2 : EtOAc 95:5 affording 0.99 g (48%) of the title compound.

^{1}H-NMR ($CDCl_3$, δ): 2.58-2.79 (m, 6H, piperazine CHs and $CONCH_2C\underline{H_2}N$), 2.92-3.08 (m, 4H, piperazine CHs), 3.85 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.79-6.99 (m, 3H, phenyl CHs), 7.63-7.77 (m, 2H, phthalimide CHs), 7.81-7.89 (m, 2H, phthalimide CHs).

2-[4-(5-Chloro-2-fluorophenyl)-1-piperazinyl]-ethylamine (29C)

A solution of 0.99 g (2.57 mmol) of the above intermediate 29B and 0.37 ml (7.70 mmol) of $NH_2NH_2 \cdot H_2O$ in 40 ml of EtOH was refluxed for 3 h. After cooling to room temperature, the precipitate was filtered off, washed with iced EtOH (30 ml), then with Et_2O (40 ml). The solution was alkalinised with 1 N NaOH (pH=8) and extracted with CH_2Cl_2 (3x15 ml). The organic phase was dried (Na_2SO_4), filtered and evaporated to dryness at reduced pressure to give 0.67 g (100%) of the desired compound as an oil.

^{1}H-NMR ($CDCl_3$, δ): 1.55 (bs, 2H, NH_2), 2.50 (t, 2H, $NC\underline{H_2}CH_2NH_2$), 2.57-2.61 (m, 4H, piperazine CHs), 2.81 (t, 2H, $NCH_2C\underline{H_2}NH_2$), 3.08-3.17 (m, 4H, piperazine CHs), 6.83-7.02 (m, 3H, phenyl CHs).

<u>8-{2-[4-(5-Chloro-2-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione</u>

The tilte compound was prepared according to the method of Example 13, using the above intermediate 29C instead of intermediate 13B and 3,3-tetramethyleneglutaric anhydride instead of succinic anhydride. Purification was carried out eluting with petroleum ether : ethyl acetate 7:3. Yield 84%; m.p. 84.5-85.5°C.

^{1}H-NMR ($CDCl_3$, δ): 1.47-1.63 (m, 4H, CH_2s of spiro ring), 1.65-1.81 (m, 4H, CH_2s of spiro ring), 2.52 (t, 2H, $CONCH_2C\underline{H_2}N$), 2.59 (s, 4H, 2 CH_2CO), 2.62-2.73 (m, 4H, piperazine CHs), 2.99-3.08 (m, 4H, piperazine CHs), 3.97 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.82-6.99 (m, 3H, phenyl CHs).

Example 30

<u>8-{2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one</u>

<u>N-{2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethyl}-phthalimide (30A)</u>

This compound was prepared according to the method described in Example 29 for intermediate 29B, but using intermediate 7A instead of intermediate 29A. Yield 26.5%.

^{1}H-NMR ($CDCl_3$, δ): 2.23 (s, 3H, CH_3), 2.61-2.79 (m, 6H, piperazine CHs and $CONCH_2C\underline{H_2}N$), 2.81-2.98 (m, 4H, piperazine CHs), 3.89 (t, 2H, $CONC\underline{H_2}CH_2N$), 6.96

(dd, 2H, phenyl H4, H6), 7.07 (d, 1H, phenyl H3), 7.69-7.79 (m, 2H, phthalimide CHs), 7.81-7.91 (m, 2H, phthalimide CHs).

2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethylamine (30B)

This compound was prepared according to the method described in Example 29 for intermediate 29C, but using intermediate 30A instead of intermediate 29B. Yield 100%.
^{1}H-NMR ($CDCl_3$, δ): 1.61 (bs, 2H, NH_2), 2.23 (s, 3H, CH_3), 2.49 (t, 2H, $N\underline{H}_2CH_2NH_2$), 2.57-2.72 (m, 4H, piperazine CHs), 2.84 (t, 2H, $NCH_2C\underline{H}_2NH_2$), 2.88-2.99 (m, 4H, piperazine CHs), 6.94 (dd, 2H, phenyl H4 and H6), 7.07 (d, 1H, phenyl H3).

8-{2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one

The title compound was prepared according to the method of Example 20, using the above intermediate 30B instead of intermediate 13B. Purification was carried out eluting with CH_2Cl_2 : EtOAc gradient from 1:1 to 4:6. Yield 62%; m.p. 94-95°C.
^{1}H-NMR ($CDCl_3$, δ): 1.42-1.52 (m, 4H, CH_2s of spiro ring), 1.66-1.74 (m, 4H, CH_2s of spiro ring), 1.80 (t, 2H, $CC\underline{H}_2CH_2NCO$), 2.24 (s, 3H, CH_3), 2.27 (s, 2H, CH_2CO), 2.57-2.76 (m, 6H, piperazine CHs and $CONCH_2C\underline{H}_2N$), 2.86-2.99 (m, 4H, piperazine CHs), 3.41 (t, 2H, $CCH_2C\underline{H}_2NCO$), 3.52 (t, 2H, $CONC\underline{H}_2CH_2N$), 6.96 (dd, 2H, phenyl H4 and H6), 7.07 (d, 1H, phenyl H3).

Example 31

8-{2-[4-(5-Chloro-2-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one

The title compound was prepared according to the method of Example 20, using intermediate 29C instead of intermediate 13B. Purification was carried out eluting with toluene / acetone gradient from 9:1 to 8.5:1.5. Yield 66%; m.p. 82-83°C.
^{1}H-NMR ($CDCl_3$, δ): 1.48-1.53 (m, 4H, CHs of spiro ring), 1.59-1.78 (m, 4H, CHs of spiro ring), 1.72 (t, 2H, $CC\underline{H}_2CH_2NCO$), 2.25 (s, 2H, CH_2CO), 2.51-2.77 (m, 6H, piperazine CHs and $CONCH_2C\underline{H}_2N$), 2.98-3.17 (m, 4H, piperazine CHs), 3.38 (t, 2H, $CCH_2C\underline{H}_2NCO$), 3.53 (t, 2H, $CONC\underline{H}_2CH_2N$), 6.81-7.01 (m, 3H, phenyl CHs).

Example 32

Determination of affinity for cloned α_1-adrenergic and 5-HT_{1A}-serotoninergic receptors by radioligand binding assay

The determination of affinity for cloned subtypes of human α_1 adrenergic receptors was performed in membranes from CHO cells (chinese hamster ovary cells) transfected by electroporation with DNA expressing the genes encoding each α_1-adrenoceptor subtype, namely α_{1a}, α_{1b} and α_{1d}.

Cloning and stable expression of the human α_1-adrenoceptor gene were performed as previously described (Testa et al., Pharmacol. Comm. 6, 79-86 (1995)). CHO cell membranes were incubated in 50 nM Tris pH 7.4 with 0.2 nM [^{3}H]prazosin, in a final volume of 1.02 ml for 30 minutes at 25°C, in the absence or presence of competing drugs (1 pM-10 μM). Non-specific binding was determined in the presence of 10 □M phentolamine. Incubation was stopped by addition of ice-cold Tris buffer and rapid filtration through 0.2% polyethyleneimine pretreated Schleicher & Schuell GF52 filters.

Genomic clone G-21 coding for the human 5-HT_{1A}-serotoninergic receptor was stably transfected in a human cell line (HeLa) (Fargin et al., J. Biol. Chem. 284, 14848-14852 (1989)). The HeLa cells were grown as monolayers in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% foetal calf serum and gentamicin (100 □g/ml), 5% CO_2, at 37°C. The cells were detached from the growth flask at 95% confluence by a cell scraper and were lysed in ice-cold 5 mM Tris and 5-mM EDTA buffer (pH 7.4). The homogenates were centrifuged at 40000 x g x 20 minutes and the membranes were re-suspended in a small volume of ice-cold 5 mM Tris and 5-mM EDTA buffer (pH 7.4) and immediately frozen and stored at –70°C until use. On the experiment day, the cell membranes were re-suspended in a buffer containing 50 mM Tris (pH 7.4), 2.5 mM $MgCl_2$, 10 μM pargyline (Fargin et al., Nature 335, 358-360 (1988)). The membranes were incubated in a final volume of 1 ml for 30 minutes at 30°C with 1.2 nM [^{3}H]8-OH-DPAT, in the absence or presence of competing test drugs; non-specific binding was determined in the presence of 10 μM 5-HT. The incubation

was stopped by addition of ice-cold Tris buffer and rapid filtration through 0.2%-polyethyleneimine-pretreated Schleicher & Schuell filters.

The inhibition of specific binding of the radioligands by the drugs was analysed to estimate the IC_{50} value by using the non-linear curve-fitting programme Allfit (De Lean et al., *Am. J. Physiol.* 235, E97-E102 (1978)). The IC_{50} value was converted to an affinity constant (Ki) by the equation of Cheng & Prusoff (Biochem. Pharmacol. 22. 3099-3108 (1973)). Data were expressed as mean of Ki.

The compounds of the invention exhibited the desired potency and selectivity at α_{1d}-adrenoceptor, as shown in Table 1.

Table 1.

Affinity (Ki, nM) of the different compounds tested for human recombinant α_1 adrenoceptor subtypes and 5-HT_{1A} receptor.

Example	Human cloned receptors			
	α_{1a}	α_{1b}	α_{1d}	5-HT_{1A}
1	128.30	9.90	0.13	36.04
2	77.88	54.08	3.25	258.10
3	125.55	193.29	2.91	69.55
4	>1000	119.18	2.38	52.31
5	119.28	168.28	10.14	275.40
6	>1000	>1000	7.56	160.30
7	190.25	26.6	0.37	134.84
8	114.06	47.54	3.72	62.22
9	503.23	17.01	0.20	29.64
10	107.73	10.05	0.18	12.07
11	479.48	447.86	15.29	803.57
12	330.51	52.89	2.21	127.84
13	91.96	86.38	7.78	>1000
14	59.82	43.35	1.23	104.10
15	68.26	83.61	3.11	>1000
16	119.60	79.62	2.65	>1000
17	186.68	13.11	0.41	206.96
18	118.74	37.57	1.50	248.19
19	786.36	915.41	16.38	432.70
20	53.80	10.62	0.11	17.43
21	27.21	15.84	1.43	91.86
25	705.70	22.75	0.31	214.00
26	-	-	0.66	40.40
27	-	-	0.96	35.33
BMY-7378	381.05	68.97	1.43	0.93

Example 33

In vitro assessment of functional antagonism for α_1-adrenoceptor subtypes

Rat aorta (α_{1D})

Thoracic aorta was obtained from Sprague Dawley rats, cut in helicoidal strips and placed in Krebs solution containing desmethylimipramine (0.1 μM), corticosterone (1 μM), propranol (1 μM) and yohimbine (0.1 μM). The strips were mounted for isotonic

tension recording in an organ bath containing the above Krebs buffer enriched and aerated constantly with 95% O_2 and 5% CO_2, maintained at 37°C and loaded with 1.5 g. After an equilibration period, the strips were primed twice with 10 μM noradrenaline, then concentration/response-to-the-agonist curves were constructed before (basal) and after 30 minutes incubation with single antagonist concentrations (response). The Schild-plot parameters were evaluated by linear-regression analysis according to Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 53-56, Springer-Verlag).

Rat vas deferens (a_{1A})

Epididymal vasa deferentia were obtained from Sprague Dawley rats and placed in Krebs solution containing cocaine (10 μM) and ß-oestradiol (10 μM). The vasa were mounted for isometric tension recording in an organ bath containing the above Krebs buffer enriched and aerated constantly with 95% O_2 and 5% CO_2, maintained at 37°C and loaded with 0.5 g. After an equilibration time, the tissues were primed with 10 □M noradrenaline, then a non-cumulative concentration/response-to-noradrenaline curve were constructed before (basal) and after 30 minutes incubation with single antagonist concentrations (response). The Schild-plot parameters were evaluated by linear-regression analysis according to Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 53-56, Springer-Verlag).

Guinea pig spleen (a_{1B})

Spleens were obtained from Hartley guinea pigs, cut in longitudinal strips and placed in Krebs solution containing desmethylimipramine (0.1 μM), corticosterone (1 μM), propanol (1 μM) and yohimbine (0.1 μM). The strips were mounted for isometric tension recording in an organ bath containing the above Krebs buffer enriched and aerated constantly with 95% O_2 and 5% CO_2, maintained at 37°C and loaded with 1 g. After an equilibration period, the strips were primed with 10 μM noradrenaline, then concentration/response-to-the-agonist curves were constructed before (basal) and after 30 minutes incubation with single antagonist concentrations (response). The Schild-plot parameters were evaluated by linear-regression analysis according to Tallarida and

Murray (Manual of Pharmacologic Calculations with Computer Programs, 53-56, Springer-Verlag).

Rabbit aorta pre-treated with cloroethylclonidine (α_{1L})

Aorta was obtained from White New Zealand rabbits, cut in rings and placed in Krebs solution containing desmethylimipramine (0.1 μM), corticosterone (1 μM), propanol (1 μM) and yohimbine (0.1 μM). The rings were mounted for isometric tension recording in an organ bath containing the above Krebs buffer enriched and aerated constantly with 95% O_2 and 5% CO_2, maintained at 37°C and loaded with 2 g. After an equilibration period, the strips were primed twice with 10 μM noradrenaline, then cloroethylclonidine (3 x 10^{-5} M) was added to the bath for 30 minutes followed by a 30-minute washing period (three times every 10 minutes). Cumulative concentration/response-to-noradrenaline curves were constructed before (basal) and after 30 minutes incubation with single antagonist concentrations (response). The Schild-plot parameters were evaluated by linear-regression analysis according to Tallarida and Murray (Manual of Pharmacologic Calculations with Computer Programs, 53-56, Springer-Verlag).

Table 2.

Functional affinity of α_1-antagonists for the different subtypes of the α_1 adrenoceptor, expressed as pK_B values

Compound	Rat aorta α_{1D}	Rat vas deferens α_{1A}	Guinea pig spleen α_{1B}	Rabbit aorta + CEC α_{1L}
BMY 7378	8.32	6.67[a]	6.55[a]	5.85
EXAMPLE 1	8.99	5.43	5.55	5.29
EXAMPLE 20	8.89	7.00	6.42	6.13

a: Eltze M., *Eur. J. Pharmacol.* 260, 211-220 (1994).

Example 34

Effects on cystometric parameters in conscious rats with infravesical outflow obstruction by partial urethral ligature.

Animals

Female Sprague Dawley rats of 225-275 g body weight [Crl: CD(SD)BR, from Charles River Italia, Calco, Como] were used. The animals were housed with free access to food and water and maintained on a forced 12 hour alternating light dark cycle at 22-24°C for at least one week, except during experiment performance.

Instruments

- Peristaltic pump, Gilson minipuls 2.
- Conventional pressure transducers (Marb P 82, Statham P23 ID or XL).
- Polygraph recorder (Battaglia Rangoni KO 380 with ADC 1/T preamplifier, San-ei Rectigraph 8k or ALFOS WK-480R with BM 614 or BM 614/2 amplifier from Biomedica Mangoni).
- Conventional isometric force transducers (Basile 7004).

Animal preparation and surgical procedure

In order to obtain a partial obstruction of the urethra, the method previously reported by Malmgren (Malmgren A. et al., J. Urol. 137, 1291-1294, 1987; Neurourol. Urodyn. 6, 371-380, 1988) was followed with minor modifications (Guarneri L. et al. Pharmacol. Res. 24, 263-272, 1991).

The rats were anaesthetised with intraperitoneal (i.p.) administration of 3 ml/kg of Equithensin solution (pentobarbital 1.215 g, chloral hydrate 5.312 g, magnesium sulphate 2.657 g, ethanol 12.5 ml, propylene glycol 49.5 ml, distilled water to 125 ml of final volume) and then the bladder and proximal urethra were exposed via an abdominal midline incision. A silk ligature was placed around the urethra and tied in the presence of an intraluminally placed indwelling polyethylene cannula with an outside diameter of 1.22 mm. After removing the polyethylene cannula, the abdominal wall was sutured and then antibiotic medication (penicillin G 200000 I.U./kg and streptomycin 260 mg/kg i.p.) was performed. After three weeks of obstruction the animals were prepared for cystometry.

Cystometrographic preparation and recordings

The animals, anesthetized as reported above, were placed in a supine position and a midline incision was made in the shaved and cleaned abdominal wall. The urinary bladder was exposed and gently freed from adhering tissues, emptied and then

cannulated, via an incision at the dome, with a polyethylene cannula (0.58 mm inside diameter and 0.96 mm outside diameter), which was permanently sutured with silk thread. For intravenous bolus injection a similar polyethylene tubing filled with physiological saline containing sodium heparin (40 I.U./ml) was inserted into the jugular vein. The cannulae were exteriorised through a subcutaneous tunnel in the retroscapular area, where they were connected with a plastic adapter, in order to avoid the risk of removal by the animal. Two days after bladder catheter implantation, the animals, fasted overnight, were placed in Bollman's cages or in particular plastic cages which allowed some lateral and back and forth movement of the rats, allowing measurements of micturition volume (MV). After a stabilisation period of 20 minutes, the free tip of the bladder cannula was connected to a pressure transducer and to a peristaltic pump for a continuous infusion of warm saline solution (37° C), into the urinary bladder. In order to shorten the time-period of saline infusion necessary to provoke micturition in the obstructed rats, a filling rate of the bladder of 10 ml/h was chosen. During infusion of saline into the bladder, the intravesical pressure signal and urine volume micturated were continuously recorded on chart polygraph. The effect of the compounds on unstable bladder was evaluated from the cystometrograms of the obstructed rats, where the number and the mean amplitude of the spontaneous bladder contractions present during bladder filling without urine emission and termed "non-voiding contractions", were evaluated in the 2 minute time before micturition. In addition, the following urodynamic parameters were investigated: bladder volume capacity (BVC), micturition pressure (MP) and micturition volume (MV). BVC (in ml) was defined as the volume of saline infused into the bladder from the start of the infusion to micturition. MP (in mmHg) was defined as the maximal intravesical pressure induced by the contraction of the detrusor during micturition. MV (in ml), defined as the volume of expelled urine during each single micturition, was recorded by means of a force displacement transducer connected to the polygraph and measuring the urine collected in a small reservoir placed under the cage. Basal values of the parameters above reported were evaluated as the mean of the values obtained in two complete and reproducible cystometrograms before treatment (time 0). Then the animals were treated intravenously

by bolus injection with the test compound under continuous infusion of saline into the bladder.

The parameter changes after compound injection (first cystometrogram and those recorded approximately after 30 and 60 minutes) were compared with the values recorded before injection (basal values).

Results

Cystometry in conscious rats with partial bladder-outlet obstruction revealed detrusor contractions during filling which are ineffective in urine expulsion (non-voiding contractions). As reported in the following table, a 0.3 mg/kg i.v. dose of the compound of Example 1 produced rapid decrease in the frequency and amplitude of the non-voiding contractions immediately after the injections. The duration of the effects was about 30 minutes on the frequency and at least 60 minutes on the amplitude. With regard to the other urodynamic parameters investigated, BVC mean values were changed by 20-30%; MV changes followed the same modifications whereas no significant changes were observed in MP values.

We may thus say that the tested product is capable of reducing contractility of the unstable bladder.

Table 3.

Cystometry in conscious rats with partial bladder obstruction of compound of Example 1 (0.3 mg/kg i.v.)

		% changes vs basal values		
Urodynamic parameter	**N**	**First cystometrogram**	**30 minutes**	**60 minutes**
NMC – F	11	-24	-38	-23
NMC – A	11	-35	-33	-38
BVC	11	26	22	30
MP	11	-2	-7	-6
MV	11	35	42	28

NMC – F (non-micturition contractions, frequency)
NMC – A (non-micturition contractions, amplitude)
BVC (bladder volume capacity)
MP (micturition pressure)
MV (micturition volume)

Effective amounts

The following represent guidelines to effective parenteral or intravenous dose ranges expressed in mg/kg of body weight per day for the compounds of the invention:

General	0.01-20
Preferred	0.02-10
Most Preferred	1-4

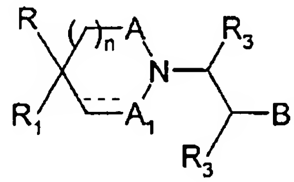
Most preferred values refer to oral dosing. Intravenous dosages should be 10 to 100 fold lower.

Selective use dosages, i.e. dosages that are active in the lower urinary tract without a substantial effect on the blood pressure, depend on the particular compound employed. Generally, in the case of a compound selective in increasing bladder volume capacity, up to four times the amount of the effective dose used can be administered without substantial effect on blood pressure. Further refinements and optimisation of dosages are possible using no more than routine experiments. The active compounds of the invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatine capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum and the like. These preparations should contain at least 0.5% of active compounds, but the amount of active ingredient may be varied depending upon the particular form and may conveniently be between 5% and about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained although the desired dosage can be obtained by administering a plurality of dosage forms. Preferred compositions and preparations according to the invention are prepared so that an oral dosage unit form contains between 1.0-300 milligrams of active compound. The tablets, pills, capsules, troches and the like may also contain, for example, the following ingredients: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, sodium

starch glycolate, cornstarch and the like; a lubricant such as magnesium stearate or hydrogenated castor oil, a glidant such as colloidal silicon dioxide; and a sweetening agent such as sucrose or saccharin may be added or a flavouring agent such as peppermint, methyl salicylate or orange flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac or other enteric-coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes, colouring and flavours. The materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used. For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but may be varied between 0.5 and about 30% of the weight thereof. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present inventions are prepared so that a parenteral dosage unit contains between 0.2 and 100 milligrams of active compound. The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or the parabens; antioxidants such as ascorbic acid or sodium bisulphite; chelating agents such as tetraacetic acid; buffers such as acetates; citrates or phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral multiple-dose vials may be of glass or plastics material. Additional compositions suitable for administration by various routes and containing compounds according to the present invention are also within the scope of the invention. Dosage forms, additional ingredients and routes of administration contemplated herein include those disclosed in U.S. Patents Nos. 4,089,969 and 5,091,182, all incorporated by reference in their entirety.

CLAIMS

1. A compound having the general formula I



(I)

wherein:

each of R and R_1 independently represents a hydrogen atom or a lower alkyl group having from 1 to 4 carbon atoms, or R and R_1 together form an alkylene bridge ($(CH_2)_{2-6}$);

n is an integer from 0 to 1;

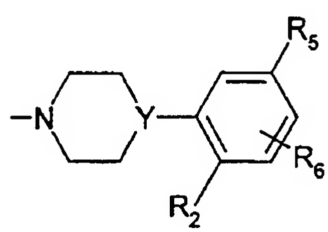
...... represents a single or a double bond;

A represents a carbonyl group or a methylene group;

A_1 represents a carbonyl group or a methylene group or a methyne group;

each R_3 independently represents a hydrogen atom or a lower alkyl group having from 1 to 4 carbon atoms;

B represents one of the following groups:



(B_1)

wherein:

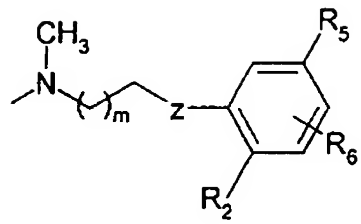
Y represents a nitrogen atom or a methyne group;

R_2 represents a halogen or a lower alkyl group having from 1 to 4 carbon atoms or a cyano group;

R_5 represents a halogen atom or a lower alkyl group having from 1 to 4 carbon atoms or a polyfluoroalkyl group or a nitro group;

R_6 represents a hydrogen or halogen atom;

wherein:



(B$_2$)

m is an integer from 1 to 3;

Z represents an oxygen or sulphur atom or an amino or methylamino group;

R_2, R_5 and R_6 have the same meanings as above;

with the proviso that not more than one of R_2, R_5 and R_6 represents a fluorine atom if R and R_1 together form an alkylene bridge, A and A_1 both represent carbonyl groups, n is 1, the heterocyclic ring is saturated and Y represents a nitrogen atom.

2. A compound according to claim 1 in which R and R_1 together represent a trimethylene, tetramethylene, pentamethylene or hexamethylene group.

3. A compound according to claim 1 or claim 2 in which A and A_1 both represent carbonyl groups, or in which one of A and A_1 represents a carbonyl group and the other of A and A_1 represents a methylene group.

4. A compound according to any preceding claim in which B represents a B_1 group, Y represents a nitrogen atom and R_2 and R_5 both represent chlorine atoms.

5. Any one of the following compounds:

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

1-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-piperidinyl-2,6-dione,

8-{2-[4-(2-Chloro-5-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]-decane-7,9-dione,

8-{2-[4-(2-Fluoro-5-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]-decane-7,9-dione,

8-{2-[4-(2,5-Dimethylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(2-Fluoro-5-trifluoromethylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(2,5-Dibromophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(5-Chloro-2-cyanophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(2-Chloro-5-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(2-Chloro-5-iodophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

3-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5.5]undecane-2,4-dione,

1-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-pyrrolidinyl-2,5-dione,

1-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-4-ethyl-4-methylpiperidinyl-2,6-dione,

2-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-2-azaspiro[4.4]nonane-1,3-dione,

7-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-7-azaspiro[3.5]nonane-6,8-dione,

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-1-methylethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(2,5-Dichlorophenyl)-1-piperidinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

N-(2,5-Dichlorophenyl)-N'-{2-(7,9-dioxo-8-azaspiro[4.5]decane-8-yl)-ethyl}-N,N'-dimethyl-1,2-diaminoethane,

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one,

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]dec-9,10-en-7-one,

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane,

8-{2-[4-(2-Chloro-5-nitrophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one N^1-oxide,

8-{2-[4-(2,4,5-Trifluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one,

3-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5.5]undecane-2-one,

3-{2-[4-(2,5-Dichlorophenyl)-1-piperazinyl]-ethyl}-3-azaspiro[5.6]dodecane-2,4-dione,

8-{2-[4-(5-Chloro-2-cyanophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one,

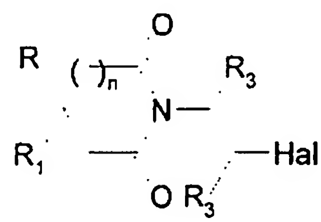
8-{2-[4-(5-Chloro-2-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7,9-dione,

8-{2-[4-(5-Chloro-2-methylphenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one and

8-{2-[4-(5-Chloro-2-fluorophenyl)-1-piperazinyl]-ethyl}-8-azaspiro[4.5]decane-7-one.

6. A pharmaceutical composition comprising a compound according to any preceding claim, or an enantiomer, diastereoisomer, N-oxide or pharmaceutically acceptable salt of such a compound, in admixture with a pharmaceutically acceptable diluent or carrier.

7. A method for the preparation of a compound having the general formula I as defined in claim 1, the method comprising alkylating an amine BH, in which B is as defined in claim 1, with a haloalkyl intermediate of the general formula II

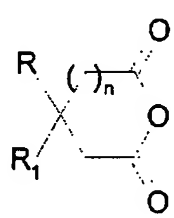


(II)

where R, R_1, R_3 and n are as defined in claim 1 and Hal represents a halogen atom.

8. A method according to claim 7 in which the reaction is carried out without solvent in the presence of a base, such as triethylamine or diisopropylethylamine, at a temperature ranging from 100 to 180°C.

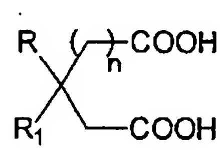
9. A method for the preparation of a compound having the general formula I as defined in claim 1, the method comprising acylating an amine $BCH_2CH_2NH_2$, in which B is as defined in claim 1, with an anhydride of the general formula



where R, R_1 and n are as defined in claim 1.

10. A method according to claim 9 in which the reaction is carried out in an apolar aprotic solvent, such as toluene, in the presence of a promoting agent, such as *p*-toluenesulphonic acid, at a temperature ranging from 80°C to the solvent's reflux temperature.

11. A method for the preparation of a compound having the general formula I in which A and A_1 both represent carbonyl groups, B represents the group B_1, R_3 represents a hydrogen atom and R, R_1, n and ...... are as defined in claim 1, the method comprising amidifying a diacid of the general formula XXI



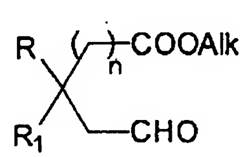
XXI

in which R, R_1 and n are as defined in claim 1, with an amine $BCH_2CH_2NH_2$ in which B is as defined in claim 1, and dehydrating the resulting amide intermediate.

12. A method according to claim 11 in which the amidification is carried out in a polar aprotic solvent, such as dimethylformamide, in the presence of a condensing agent, such as dicyclohexylcarbodiimide, at a temperature ranging from 10 to 40°C.

13. A method according to claim 11 and claim 12 in which the dehydration is effected using an anhydride, such as acetic anhydride, without solvent, at a temperature ranging from 80 to 120°C.

14. A method for the preparation of a compound having the general formula I in which A represents a methylene group, B represents the group B_1 or B_2, R_3 represents a hydrogen atom and A_1, R, R_1, n and ...... are as defined in claim 1, the method comprising reacting an ester aldehyde of the general formula XXII



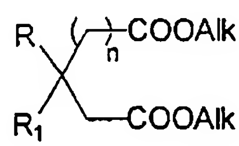
XXII

in which R, R_1 and n are as defined in claim 1, with an amine $BCH_2CH_2NH_2$ in which B is as defined in claim 1.

15. A method according to claim 14 in which the reaction is carried out under reductive conditions using a metal borohydride, such as sodium borohydride, in a polar protic solvent, such as methanol, at a temperature ranging from –5 to 25°C, to give a compound of formula I in which ...... represents a single bond and A_1 represents a methylene group.

16. A method according to claim 14 in which the reaction is carried out in an apolar aprotic solvent, such as toluene, in the presence of an acid catalyst, such as *p*-toluenesulphonic acid, at the solvent's reflux temperature, to give a compound of formula I in which ...... represents a double bond and A_1 represents a methyne group.

17. A method for the preparation of a compound having the general formula I as defined in claim 1, the method comprising condensing a diester of the general formula



where R, R_1 and n are as defined in claim 1 with an amine $BCH_2CH_2NH_2$ in which B is as defined in claim 1.

18. A method according to claim 17 in which the condensation is effected without solvent at a temperature ranging from 80 to 160°C.

19. A method for the preparation of a compound having the general formula I in which A and A_1 both represent methylene groups, ... represents a single bond and B, R, R_1, R_3 and n are as defined in claim 1, the method comprising reducing a compound having the general formula I in which A and A_1 both represent carbonyl groups and B, R, R_1, R_3, n and ...... are as defined in claim 1.

20. A method according to claim 19 in which the reduction is effected using a metal borohydride, such as sodium borohydride, in the presence of a Lewis catalyst, such as boron trifluoride etherate, in a polar aprotic solvent, such as tetrahydrofuran, at a temperature ranging from –5 to 25°C.

21. A method for the treatment of micturition problems associated with unstable bladder, the method comprising administering an effective amount of a compound according to any of claims 1 to 5 to a patient suffering from such problems.

22. A method for the treatment of cardiovascular problems due to skeletal muscle arteriole constriction or to abnormal smooth-muscle cell proliferation, the method comprising administering an effective amount of a compound according to any of claims 1 to 5 to a patient suffering from such problems.

23. A method according to claim 21 or claim 22 in which the compound is administered in an amount of from 0.01 to 20 mg/kg/day.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/06738

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D211/88 C07D207/40 C07D209/54 C07D221/20 C07D401/06 A61K31/4015 A61K31/4545 A61K31/403 A61K31/438 A61P9/10 A61P13/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 00 04012 A (NOBLE STEWART ;WETZEL JOHN M (US); CRAIG DOUGLAS A (US); KONKEL MI) 27 January 2000 (2000-01-27) example 13 page 30, line 14 -page 31, line 5	1-8, 21-23
A	EP 0 911 330 A (COUNCIL SCIENT IND RES) 28 April 1999 (1999-04-28) page 4, example (a) and (h)	1-6, 21-23

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 November 2000	04/12/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Seitner, I

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MARIA L. LOPEZ-RODRIGUEZ: "1-'omega-(4-Arylpiperazin-1-yl)alkyl!-3-diphenylmethylene-2,5-pyrrolidinediones as 5HT1A Receptor Ligands: Study of the Steric Requirements of the Terminal Amide Fragment on 5-HT1A Affinity/Selectivity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 8, 1998, pages 581-586, XP002924834 example 3H -----	1-6, 21-23

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/06738

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0004012 A	27-01-2000	AU 5214699 A	07-02-2000
EP 0911330 A	28-04-1999	NONE	